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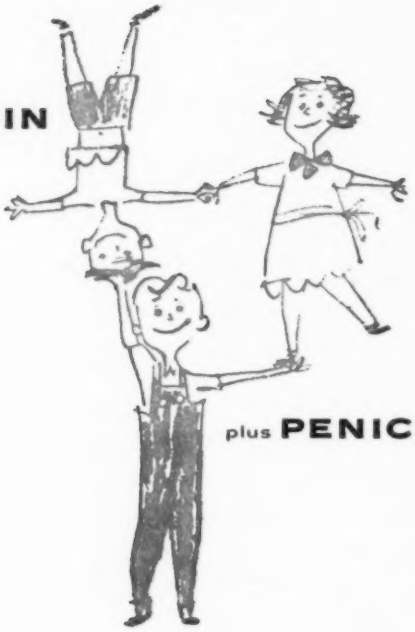

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**Crump, E. P.: Postgraduate Med., 13:552, 1953*

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The Journal of Pediatrics

VOL. 44 APRIL, 1954 NO. 4

THE PROPHYLAXIS AND TREATMENT OF BACTERIAL COMPLICATIONS OF MEASLES WITH BENZETHACIL AND AQUEOUS PROCAINE PENICILLIN G

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NEW YORK, N. Y.

PROPHYLAXIS with convalescent serum, immune adult serum or plasma, placental or blood globulins, especially gamma globulin, is very efficient in eliminating all but 1 to 2 per cent of the complications of measles.[1, 2] Furthermore,[3] the immunity resulting from the attack of modified measles is long lasting in most individuals. Of the various products available for measles prophylaxis, gamma globulin is by far the choice and is generally preferred.

The demonstration[4] that gamma globulin may modify or prevent poliomyelitis has resulted in the temporary withdrawal of most of the gamma globulin from the market. While gamma globulin will be available for measles prophylaxis through local health departments it will not be possible, at least not in the immediate future, to obtain it from the corner drugstore. In all probability the greater difficulty in obtaining gamma globulin will result in the omission of measles prophylaxis in many instances. It is important, therefore, to evaluate the treatment of measles with available therapeutic agents in hope that these drugs may minimize the morbidity and the mortality associated with the disease.

It has been demonstrated by Holbrook[5] and Coburn[6] that the sulfadiazine treatment of measles is effective in eliminating bacterial complications. Penicillin and Aureomycin were shown to be very effective in eliminating bacterial complications of measles by Karelitz and associates.[7]

Since a single injection of Benzethacil[8] was shown to yield blood levels of penicillin sufficient to eliminate *Hemolytic streptococcus* from the nasopharynx of children with rheumatic fever for two or four weeks, and since many of the measles complications are caused by *H. streptococcus*, the study of the clinical effect of a single dose of Benzethacil in the treatment of measles seemed indicated. As a control study alternate children were to be treated with daily injections of 300,000 units of aqueous penicillin, and a third group was to serve as the untreated controls.

From the Willard Parker Hospital.

The Benzethacil was donated for this study by Wyeth, Incorporated.

The aqueous procaine penicillin G was donated for this study by Eli Lilly & Co., and E. R. Squibb & Sons.

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The patients were treated with Benzethacil, aqueous procaine penicillin, or served as untreated controls in order of their admission to the hospital, except that the patients having complications were alternated in the two penicillin groups. This caused the antibiotic-treated groups to be weighted with complications and thereby a more severe test was placed on them.

One-hundred seventy patients were observed from January to April, 1953. Sixty-one were given Benzethacil, a single injection of 600,000 units for children under 5 years of age, and 1,200,000 units for those 5 years or over. Sixty-seven children received 300,000 units aqueous procaine penicillin on admission and daily for a total of four doses. Forty-one children received no therapy unless complications developed, when suitable treatment was promptly instituted.

TABLE I. DISTRIBUTION OF CASES ACCORDING TO AGE

GROUP	AGE (YEARS)												TOTAL
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-15	OVER 15	
1. Benzethacil	14	20	9	4	4	3	1	0	2	1	0	3	61
2. Aqueous procaine penicillin	9	17	17	6	7	7	2	0	1	0	1	0	67
3. Untreated	6	9	11	10	1	2	1	0	0	1	0	0	41
4. Aqueous procaine penicillin, 600,000 units 1st, 3rd, and 6th day	8	14	11	7	2	3	0	1	1	0	0	0	47
5. Untreated	10	4	11	5	3	3	3	0	1	0	0	0	40

TABLE II. DAYS OF ADMISSION RELATED TO APPEARANCE OF RASH (R)

GROUP	R-2	R-1	R	R+1	R+2	R+3	TOTAL
1. Benzethacil	1	0	34	20	4	2	61
2. Aqueous procaine penicillin G	1	0	28	28	9	1	67
3. Untreated	0	0	16	22	4	0	42
4. Aqueous procaine penicillin, 600,000 units 1st, 3rd, and 6th day	0	0	20	21	4	2	47
5. Untreated	0	0	12	20	6	2	40

Shortly after the investigation was begun it was noticed that some of the children were unhappy because of the local discomfort produced by the Benzethacil. It was therefore decided to investigate the effect of 600,000 units of aqueous procaine penicillin injected every second or third day until the temperature remained normal for two days. A fifth group were to serve as controls for Group 4.

An additional eighty-seven cases were observed in April and May, 1953. Forty-seven of the children (Group 4) were injected on admission with 600,000 units of aqueous procaine penicillin G. This was repeated two days later and again three days thereafter, or on the first, third, and sixth day after admission. Alternate patients (Group 5) were left

untreated as controls, except that those admitted with manifest bacterial complications were placed in the treated group.

In evaluating the duration of fever it seemed to us that a reasonably accurate comparison might be had if the day of the first appearance of the rash was considered as the first day of fever. If a child was admitted on the second day of rash it was assumed that the child was febrile one day before admission. The highest temperature recorded on the day of admission was taken as the highest temperature of each day from the time of onset of rash to the time of admission to the hospital.

The diagnosis of pneumonia was made on clinical grounds and in almost all instances confirmed by radiography. Otitis media was of the catarrhal type. No instance of purulent otitis media with perforation of the eardrum was noted.

Since the patients were discharged from the hospital after two to three days of normal temperature unless complications were present, we are unable to discuss the question of late complications.

The age distribution of the patients in each group is well balanced (Table I), even though on admission no attempt was made to separate the patients into various age groups. Likewise the groups were fairly well divided with patients in whom the rash appeared one or two days before admission, etc. (Table II).

RESULTS

There was no noticeable effect of treatment on the duration or severity of the rash. There was no demonstrable difference in the degree or duration of photophobia between the treated and the control groups. There was little difference in the group treated with 300,000 units of aqueous procaine penicillin daily, or 600,000 units on alternate days. Two complications followed Benzethacil treatment; no complications developed in the two procaine penicillin groups.

The differences observed between the treated and control groups were primarily in the incidence of complications and in the duration of fever, results almost identical with those previously[7] observed when aqueous procaine penicillin and Aureomycin were compared with untreated controls in their efficacy in treatment of bacterial complications of measles.

Of the sixty-one patients in Group 1 (Table III), or those treated with Benzethacil, eleven had catarrhal otitis media on admission, and two had pneumonia. One patient developed pneu-

TABLE III. MEASLES. COMPLICATIONS OBSERVED BEFORE AND AFTER TREATMENT

	BENZETHACIL		AQUEOUS PROCAINE PENICILLIN 300,000 U DAILY × 4		UNTREATED		AQUEOUS PROCAINE PENICILLIN 600,000 U × 3		UNTREATED	
COMPLICATION	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
Catarrhal otitis media	11	0	14	0	0	3	8	0	0	1
Pneumonia	2	1	6	0	0	8	11	0	0	4
Diarrhea	0	0	0	0	0	1				
Bacteremia	0	1	0	0	0	0				
No. of cases	61		67		41		47		40	

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monia five days after the injection of Benzethacil (Case 1).

CASE 1.—E. A., a 22-month-old white female infant, was admitted on April, 1, 1953, because of fever for four days, cough for one day, and a rash over the face and body for one day. She received one injection of 300,000 units of aqueous procaine penicillin and one injection of 2 c.c. of gamma globulin prior to her admission to Willard Parker Hospital.

Physical examination on admission: She was acutely ill. The temperature was 102.4° F.; pulse 100; respiration 24. A typical morbilliform maculopapular rash was present on the face and body. There was a mild conjunctivitis and photophobia. The eardrums were slightly pink. Koplik's spots were noted. Both tonsils and pharynx were injected. Chest revealed no impaired resonance. Breath sound was clear except for a few rhonchi in the entire left lung.

The patient received one injection of Benzethacil 600,000 units intramuscularly on admission. The temperature was septic, reaching 104° F. daily for one week. Definite moist râles were audible in both lung fields on the sixth hospital day. A diagnosis of bronchopneumonia was confirmed by roentgenologic study. She was treated with aqueous penicillin 100,000 units intramuscularly every three hours. The temperature became normal on the next day, and her chest condition was cleared up within three days. She was discharged in good condition on the twelfth hospital day.

The nose and throat culture taken on admission revealed alpha hemolytic streptococcus, *N. catarrhalis*, and yeast cells. A blood culture taken during the illness April 7 was negative.

Another child developed symptoms of a *Staphylococcus aureus* sepsis on the fourth day after treatment with Benzethacil (Case 2).

Case 2.—E. C., a 2½-year-old Puerto Rican girl, was admitted to Willard Parker Hospital on April 6, 1953, with a rash for one day. Detailed information of her illness was unobtainable.

Physical examination on admission: She was acutely ill and slightly drowsy. There was an extensive morbilliform maculopapular rash all over the body. A few cervical glands were palpable. The conjunctivae were slightly injected. The eardrums were pink. Both tonsils were enlarged and reddened. Koplik spots were present on the buccal mucosa. Chest showed no impaired resonance. Breath sound was slightly harsh in nature. Rhonchi were audible in both lung fields.

She received one injection of Benzethacil 600,000 units intramuscularly on admission, but the temperature remained elevated for the next four days (around 104° F.). On April 10 (fourth hospital day) she had a fading morbilliform eruption with fine scaling. There were two hemorrhagic vesicles on the posterior aspect of the left thigh and upper left leg about 3 or 4 mm. in diameter and each surrounded by erythema. The lips were swollen and covered with confluent vesicles. A few vesicles were present on the tongue. Both tonsils were swollen and covered with exudate. Here and there on the trunk there were tiny pin-point-sized excoriated papules or vesicles, some covered with minute crusts. It was our impression at the time this child had a bacteremia stomatitis and tonsillitis, probably due to *Staph. aureus*, since that organism was recovered from the nose and throat, skin, eye, and mouth on April 9. Cultures of the left eye, nose, and throat taken on April 11 revealed *Staph. aureus* and alpha hemolytic streptococcus. Unfortunately, no sensitivity studies were obtained.

The patient received intramuscular injections of aqueous procaine penicillin and oral Terramycin for three days and then oral Aureomycin and intramuscular injections of aqueous procaine penicillin for one week. The child became afebrile on the seventh hospital day, two days after the above

treatment was started, and improved steadily. She developed typical varicella eruptions on the fifteenth hospital day. The course was mild and uncomplicated.

Of Group 2, consisting of sixty-seven children who received 300,000 units of penicillin intramuscularly daily, there were fourteen instances of catarrhal otitis media and six of pneumonia, all of whom recovered under treatment. No bacterial complications developed later.

Of the forty-one cases in Group 3, or the untreated complicated cases, three developed otitis media, eight pneumonia, and one diarrhea. All responded to penicillin or broad spectrum antibiotics or combinations of the two, introduced as soon as the complications were detected.

Group 4, the forty-seven who received 600,000 units aqueous procaine penicillin three times in six days, did very well. Eleven of the forty-seven had pneumonia and eight catarrhal otitis media on admission. All of these were cured, whereas in Group 5, of the forty patients who served as controls for Group 4, four developed pneumonia and one bilateral catarrhal otitis media. These complications responded to penicillin therapy.

Table IV reveals the distribution of complications in the various age groups. The findings are as might have been expected, the greatest incidence of complications was in the first five years, more especially in the first two years when the danger is greatest. Complications were present in 27.6 per cent of the patients before antibiotic treatment was started.

The fever lasted 3.16 days in the

TABLE IV. INCIDENCE OF COMPLICATIONS ACCORDING TO AGE

	AGE (YEARS)							
	0-1	1-2	2-3	3-5	5-9	9-15	OVER 15	TOTAL
Groups 1-3								
No. of patients	29	46	37	32	19	3	4	170
No. of complications	10	17	9	9	2	0	0	47
Percentage	34.4	36.9	24.3	28.1	10.5	0	0	27.6
Groups 4-5								
No. of patients	18	18	22	17	12	0	0	87
No. of complications	5	7	8	3	1	0	0	24
Percentage	20.8	29.2	33.3	12.5	4.2	0	0	27.6
Groups 1-5								
No. of patients	47	64	59	49	31	3	4	257
No. of complications	15	24	17	12	3	0	0	71
Percentage	31.9	37.5	28.9	24.5	9.7	0	0	27.6

TABLE V. MEASLES. PERCENTAGE OF PATIENTS WHOSE TEMPERATURE WAS 100° F. OR OVER, BEGINNING WITH DAY OF RASH

	DAYS:						
	1	2	3	4	5	6	7
1. Benzethacil (61 cases)	100	95.0	72.0	28.0	9.8	4.9	1.64
2. Aqueous procaine penicillin 300,000 U daily × 3 (67 cases)	100	95.5	65.5	31.4	7.6	11.1	1.5
3. Controls (42 cases)	100	91.0	88.0	76.0	50.0	33.3	7.2
4. Aqueous procaine penicillin 600,000 U × 3 (47 cases)	100	89.4	65.9	36.2	25.5	6.4	4.3
5. Controls (40 cases)	100	92.5	70.0	40.3	15.0	15.0	2.5

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Benzethacil group, 3.23 days in the aqueous procaine penicillin treated group, and 4.38 days in the control group. The difference in duration of fever between the treated and control groups previously reported was more nearly two days, or greater than that observed in this study. This may be due to the fact that more patients were observed in the preeruptive stage of measles in the first[7] study and therefore treatment was instituted earlier in relation to the time of appearance of the rash and the development of pneumonia or otitis media.

SUMMARY

One of the infections which was not prevented or which failed to repond to Benzethacil was due to *Staph. aureus*. Since an increasing number of strains of *Staph. aureus* is found to be penicillin resistant, the failure to control this infection is not surprising, and suggests the need for more extensive penicillin treatment or other antibiotics in some cases of measles. Likewise, the pneumonia which developed in a Benzethacil-treated patient suggests an etiological agent which was not susceptible to the penicillin concentration created by the Benzethacil.

The fact that a single injection of Benzethacil was effective in fifty nine out of sixty-one cases and that penicillin injections given on alternate days was effective in all forty-seven cases, is however, quite significant. It is most important in the management of measles in hospitals since the need for nursing care as well as that of a physician is thereby sharply reduced. This is particularly welcome at a time when the shortage of nurses and house doctors is so acute. Furthermore it enables one to treat measles from the outpatient departments of hospitals provided adequate follow-up by doctors or visiting nurses is available to detect possible complications.

The fear of measles even if not modified by gamma globulin is sharply reduced by the knowledge that most complications can be avoided. While the morbidity is greater in measles treated by antibiotics than in measles modified by passive immunity through prophylaxis, it is conceivable that the former may result in greater or longer lasting immunity.

Encephalitis was not observed in the 255 patients studied, as was the case in the 135 patients previously observed.[7] This is probably not significant since measles encephlitis may be as uncommon as one in one to four thousand cases. It is not likely that measles encephalitis will be prevented by penicillin or other antibiotic therapy if the current interpretations of the etiology of measles encephalitis are correct. The practical answer to this question will become known only after very large numbers of antibiotic-treated patients are compared to untreated patients.

CONCLUSIONS

1. Of sixty-one measles patients who received a single injection of Benzethacil, 600,000 units in children less than 5 years of age, and 1,200,000 units in children 5 years or older, only two developed bacterial complications.

2. No complications were observed in sixty-seven patients subsequent to four daily injections of 300,000 units

of aqueous procaine penicillin, or in forty-seven cases after treatment with 600,000 units of aqueous procaine penicillin on alternate days.

3. The results following treatment with both the Benzethacil and aqueous procaine penicillin were in striking contrast to the controls, of whom 27.6 per cent developed bacterial complications, mainly pneumonia.

4. The fever of the treated groups was of shorter duration than in the control cases of measles.

5. While measles prophylaxis with gamma globulin is most desirable, it is now adequately demonstrated that most complications can be avoided by antibiotic therapy.

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HEREDOFAMILIAL INFANTILE CEREBRAL DEGENERATION: THE RELATIONSHIP OF SYSTEMIC FACTORS TO THE PATHOGENICITY

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IT IS the purpose of this study to attempt a correlation between the biochemical and pathological features of a poorly understood neurological entity and in so doing to present a rather new and reasonable approach to the pathogenesis of this disorder.

The group of disorders classified as cerebral degenerations often give rise to similar pathological changes but may be characterized by markedly different clinical manifestations. The large number of such patients appear rather unaffected by such a process at birth, but once the process becomes manifest it will usually present a progressive course. The family level of involvement seems to be rather constant in regard to the age of onset of symptoms, but there can be definite variations in the age of onset in different generations. The term "law of anticipation" has been applied to these circumstances in which succeeding generations show an earlier age of onset of symptoms. Abiotrophy is a term applied by Sir William Gowers to a primary nervous system disorder which was able to overcome the local tissue resistance with consequent disintegration of that tissue. There is more than suspicious evidence that the term *primary* in the nervous system is misleading, and that actually one deals with a primary disorder of metabolism with a *secondary* nervous system degeneration. Classical examples of this would be found in pernicious anemia with its subacute combined sclerosis, diabetes mellitus with its attendant peripheral neuritis, Gaucher's disease, Niemann-Pick's disease, and Schüller's-Christian disease, all with an associated disturbance of lipid metabolism, as well as hepatolenticular degeneration. There is a form of polyneuritis which has been observed in hematoporphyrinuria.

The patients who served as the basis for the present writing were not all observed by us, and in some instances old hospital records were consulted which were very incomplete. This fact assumed less significance as it became apparent that the pattern of illness was quite definable, and, even more, that the course of the disease became predictable as new members of the family were observed.

Family 1.—T. J. S. was admitted to the Methodist Hospital, Indianapolis.

Presented at the Postgraduate Pediatric Conference, State University of Iowa, Iowa City, Iowa, Sept. 17, 1953.

This study was aided by a grant from the Charles J. Wolf Foundation for Medical Research, Indianapolis, Ind.

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Ind., on June 13, 1947, at which time he was 2 months of age. He had developed diarrhea at the age of 6 days but he was apparently well one week later. Obstipation occurred then and frequent enemas became necessary. The diarrhea recurred three weeks later and was accompanied by projectile vomiting. He became lethargic, developed generalized body rigidities, the red blood count was 2.79 million, and the white blood count was 21,200 per each cubic millimeter of blood. Spinal tap was not successful. One blood culture was positive for *Streptococcus hemolyticus*, and routine agglutinations for typhoid fever, paratyphoid fever, and brucella were negative. The tuberculin test was negative.

TABLE I. CLASSIFICATION OF THE HEREDOFAMILIAL AND DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM*

A. Abiotrophies with diffuse and focal degeneration affecting chiefly the white matter.
   1. Massive focal lesions in the cerebral white matter involving the myelin sheath first and softening later.
      Encephalitis periaxialis diffusa.
   2. Large spherical lesions composed of concentric globes of demyelination separated by zones of intact myelin.
      Encephalitis periaxialis concentrica.
   3. Diffuse and symmetrical degeneration of the cerebral white matter without softening.
      Cerebral sclerosis of Pelizaeus-Merzbacher (chronic infantile)
      Cerebral sclerosis of Scholz (subacute juvenile)
      Cerebral sclerosis of Krabbe (acute infantile)
   4. Focal degenerations of both brain and spinal cord involving the gray matter as well as the white matter and sometimes causing complete softening.
      Neuromyelitis optica.
   5. Focal degenerations involving both white and gray matter chiefly in the spinal cord and brain stem, but also in the cerebral hemispheres with myelin destruction and dense gliosis but without softening and without great injury to the axis cylinders.
      Chronic disseminated sclerosis.
   6. Disseminated areas of encephalomalacia resulting in cavity formation involving primarily the subcortical white matter but later invading and destroying the cortex.
      Disseminated encephalomalacia with cavity formation.

B. Abiotrophies involving the cerebral gray matter.
   Degeneration of the cerebral gray matter (Alpers)
   Familial cerebral calcification (Penfield)

*From Ford: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Charles C Thomas, Publisher.

and fluctuating fever was recorded. Anorexia was marked and the temperature curve remained elevated. There were daily spikes to 105° F.

The birth history was essentially negative.

Examination of the baby led to the findings of severe dehydration and obvious generalized body rigidity. The infant was apathetic and cried at the slightest touch of the examiner.

X-ray studies of the chest and skull were normal. Three separate urine samples were normal. The hemoglobin was 7.5 grams per 100 c.c. of blood.

The infant did not respond to therapy which consisted of repeated blood transfusions and intramuscular penicillin. He was dismissed on Aug. 3, 1947, and readmitted on Dec. 4, 1947, at which time he presented a picture of severe acidosis and dehydration occasioned by recurrence of the diarrhea. The temperature was normal at this time. The spinal fluid examination showed 14 red blood cells, protein of 162 mg. per cent, and a glucose of 31 mg. per cent. Another blood culture was positive for *Str. hemolyticus*. Death occurred on Dec. 8, 1947; tem-

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perature was 105° F. at that time. Autopsy was not done.

M. J. O'C., aged 2 months, was admitted to St. Vincent's Hospital, Indianapolis, Ind., on April 9, 1950. It was stated that the infant was not able to retain any type formula. Weight gain had been nil, and at the time of admission the weight of 9¼ pounds represented a gain of only ½ pound over the birth weight. The infant appeared apprehensive and generalized to sudden recurrence of loss of tissue elasticity. The fever and the vomiting persisted.

He was readmitted on July 6, 1950, after one month of comparative well-being at home. The projectile vomiting had recurred. Examination showed no change from the previous observations which had included dehydration, pallor, and spasticity. The temperature curve spiked to 103° F. daily.

Fig. 1.

rigidities were noted. The temperature curve was consistently elevated, with daily spikes to 104° F. The response to parenteral fluids was very poor, and the infant continued to vomit even skimmed milk. The hemoglobin was 10.6 grams per 100 c.c. of blood, the red blood count was 2.88 million, and the white blood count was 12,000 per cubic millimeter of blood.

The infant continued to show remarkable weight fluctuations related

This child is now 3½ years of age and weighs 13 pounds. There is generalized body rigidity (Fig. 1).

M. G. O'C. was born on Dec. 8, 1951, and his weight at birth was 10¼ pounds. He appeared normal at birth and was observed very closely. The blood count and urine examination made within three hours after birth were normal, but forty-eight hours after birth he developed pallor and fever to 102.4° F. The hemoglobin

was found to be 9.4 grams per 100 c.c., the red blood count was 3.48 million, and the white blood count 16,500 per cubic millimeter of blood. Bleeding and coagulation times were normal. A blood culture was negative. A sedimentation rate was 2 mm. per hour, and the spinal fluid was totally negative. Penicillin and streptomycin therapies were begun and the infant was given parenteral fluids since he showed dehydration as a consequence of his projectile vomiting. Periodic episodes of rigidity were noted. There was evidence of pneumonia and otitis media on Jan. 4, 1952, in spite of therapy, and death occurred eleven days later.

Necropsy findings included extensive bilateral pneumonia, bilateral otitis media, and necrosis of both adrenal glands. Culture from the lungs showed coliform bacilli, and gram-negative diplococci were recovered from the ears.

The brain hemispheres were symmetrical and normal in consistency. The gyri were prominent though the sulci were of the usual depth. No alterations were noted in the circle of Willis or other arteries. The gray matter was normal in width, color, and distribution in all regions of the cerebral hemispheres. The white matter had a grayish and somewhat translucent appearance. There was no change in the ventricles or choroid plexus. The markings of the pons were less distinct than usual but those of the medulla appeared normal. There was less differentiation between the gray and white matter of the cerebellum than usual. A portion of the upper cervical spinal cord had a normal gross appearance.

Sections from each lobe of the cortex as well as the basal ganglia, pons, medulla, and cerebellum were prepared with hematoxylin and eosin stain, Nissl's stain (cresol violet), Mallory's phosphotungstic acid-hematoxylin stain, and with Sudan black.

The outstanding feature noted in all areas was an extreme loss of myelin in the white matter with relative preservation of the gray matter of the brain. The loss of myelin was accompanied everywhere by a definite and conspicuous proliferation of astrocytes. Oligodendroglia, while present in all regions of the white matter, were reduced in number. Scattered microglia were found but there was no formation of compound granular corpuscles.

The gray matter appeared intact throughout the cerebral cortex. There was no necrosis or other alteration in the nerve cells, which were normally arranged in architectonic layers. The oligodendroglia were numerous and showed acute swelling. No reaction was noticed in the astrocytes or microglia, and the hippocampal cells were intact. The general architecture was well preserved in sections of the basal ganglia, and no loss or degeneration of nerve cells was noted. The internal capsule was relatively well myelinated but not completely so, and was free of astrocytic proliferation. The ependyma was intact; however, underneath it there was a layer of incompletely differentiated glial cells of the type and extent expected in a slightly immature brain.

The corticospinal tracts took the myelin stain well, though the tracts were somewhat reduced in relative volume. Good myelin staining was obtained in the ventral spinocerebellar tracts. The remainder of the pontine tracts stained poorly for myelin or not at all. There was no gliosis. The ganglion cells of the medulla were well preserved.

The central portions of the white matter of the cerebellum were well myelinated but in the outer portion myelin was lost. The cellular components of the cerebellum showed no evidence of degeneration. There was a persistent but narrow external granular layer. The blood vessels were normal throughout the brain.

There was no evidence of perivascular cuffing. There was a slight increase in fibrous tissue associated with a mild infiltration of mononuclear cells

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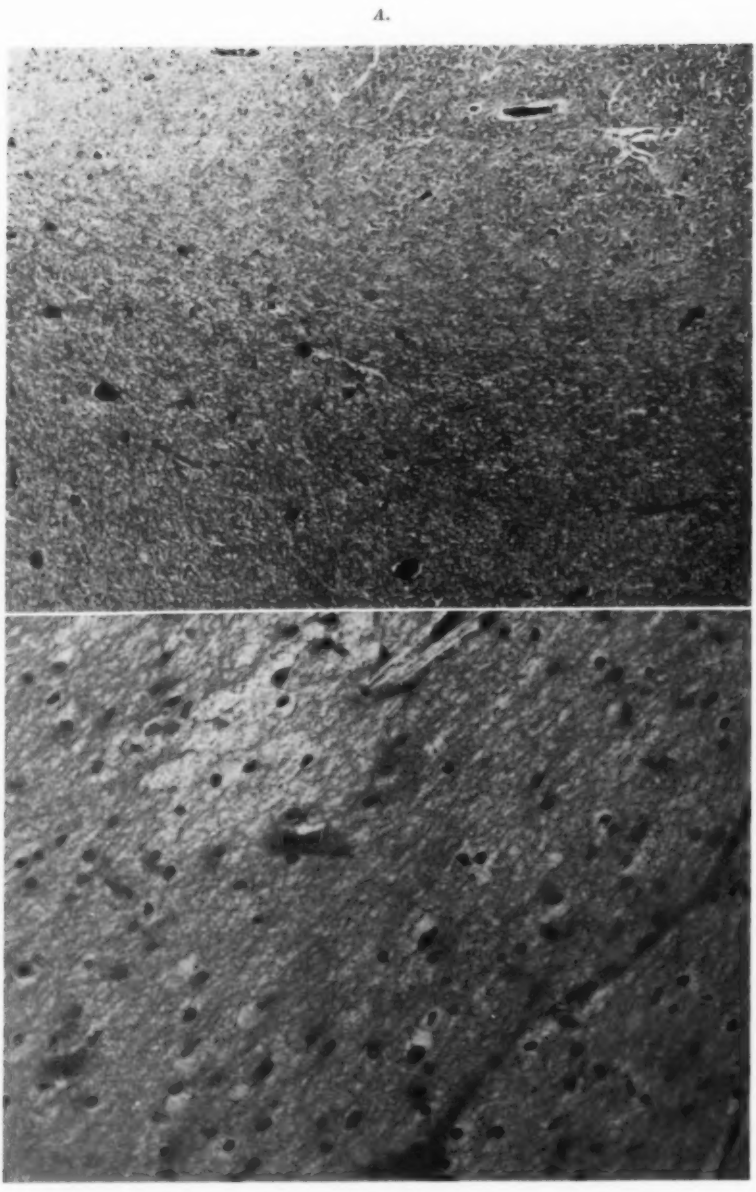

A.

B.

Fig. 2.—Cerebral cortex, M. G. O'C. *A*, Sudan black stain showing loss of white matter in cerebral cortex. (×110.) *B*, H & E stain showing disruption of structures. (×110.)

and a few lymphocytes in the leptomeninges. No evidence of an acute inflammatory reaction was present in any part of the brain.

*Family 2.**—The following data were contributed by Dr. Paul G. Meyers of Manchester, Iowa. Mrs. T., the maternal grandmother, and Mrs. F., the mother of the children, had always been in good health. Neurological disease was unknown in the family.

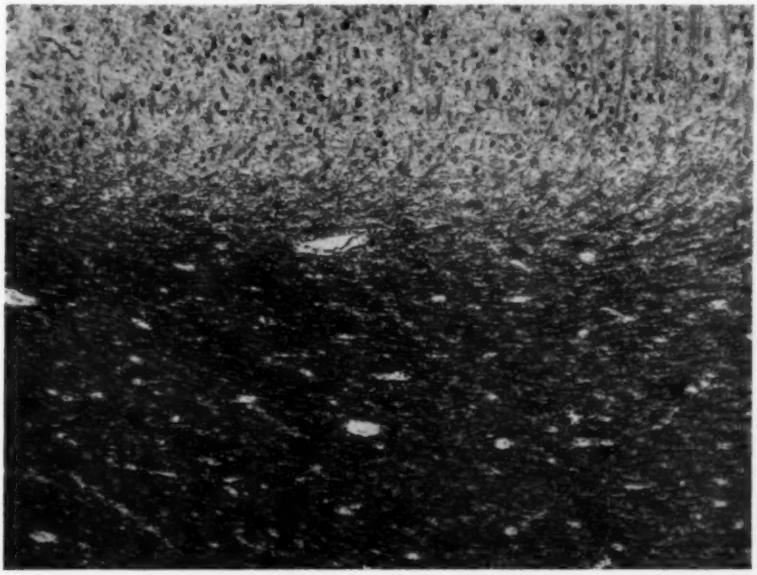

Fig. 3.—Cerebral cortex, A. F. Sudan black stain showing preservation of myelin in the white matter. (×110.)

A. F. was born on Sept. 27, 1947, and was well until he developed convulsions at the age of 4 years. The seizures were not well controlled through the use of anticonvulsant drugs. He developed dysphagia and died on Dec. 1, 1952, of starvation and terminal pneumonia. M. F. was born on Nov. 30, 1948. She developed convulsions during April of 1952. Six months later she lost her ability to walk and suffered from emotional outbursts.

The report of the anatomical findings in the case of A. F. made by one of us (O. T. B.) follows:

Each block of cerebral cortex showed a distinct demarcation of gray and white matter. The white matter was normal in texture and the gray matter had its usual appearance.

Each block was stained with hematoxylin and eosin stain and Sudan black. There was some disruption of the architectonic layers in the cerebral cortex. The nerve cells were normal in general outline, their nuclei were intact, but their cytoplasm had a homogenous appearance in hematoxylin and eosin stained sections. Vacuolation was absent. The cytoplasm of the nerve cells stained black intensively and selectively and their nuclei remained free of stain in sections

*Complete data relating to this family will be published at a later date by staff members, Department of Neurology, State University of Iowa.

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stained with Sudan black. Material which stained with Sudan black was found in some astrocytes and occasionally in some microglia and oligodendroglia. There were focal areas of gliosis from which the nerve cells had disappeared; some of these areas were large but others consisted of small foci.

Myelination was complete and well preserved in all sections of the white matter and there was no gliosis. The meninges were somewhat more vascular than usual but otherwise not remarkable.

The Purkinje cells were reduced in number in the cerebellum and those seen contained material which stained with Sudan black. The white matter was well myelinated throughout. There was a very marked reduction in the granular layer with glial replacement.

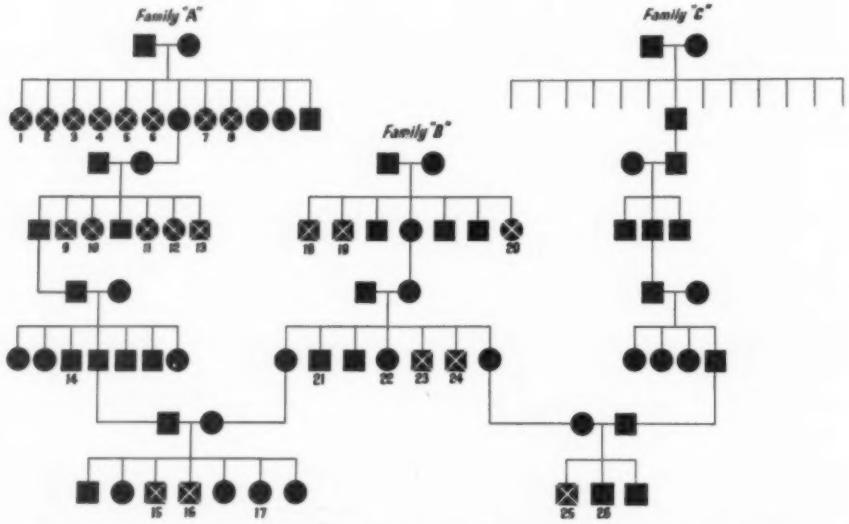

Fig. 4.—Family 1. It will be noted that the babies involved here are the offspring of sisters who, though themselves normal, are carriers of the disease which is recessive and sex linked. The same applies to the maternal grandmother who at the age of 62 years recalls no important illness during her entire lifetime. It will be noted that Mrs. D., the maternal grandmother, had lost two male infants from an identical illness which had been marked by diarrhea and fever. The pathological findings were those of otitis media and pneumonia, but unfortunately brain examination was neglected. Emaciation and body rigidity were part of the picture in each illness, and these factors help to correlate the disease with the illness pattern which is further described.

Male. Female. Male, died. Female, died.

1-8, Died in infancy, cause unknown. Sex unknown. *9*, Brain fever when 11 months old. *10*, Pertussis when 11 months old. *11*, Brain fever when 16 months old. (Walked and talked normally.) *12*, Congenital hydrocephalus. *13*, Osseous tuberculosis. *14*, Schizophrenia, 20 years old. *15*, Fever and gastric symptoms at age of 3 days. *16*, Prolonged fever and malnutrition since birth. *17*, Now febrile and malnourished, weighed 17 pounds at 15 months. *18*, Accident at age of 3 years. *19*, Breech delivery. *20*, Miscarriage, cause unknown. *21*, Prolonged fever after birth, malnourished and mentally retarded. (Walked at 2 years of age.) *22*, Mentally retarded after accidental brain injury at age of 33 years. *23*, Fever and malnutrition since birth. Died at age of 5 months. *24*, Fever and malnutrition since birth. Died at age of 10 months. *25*, Fever, spasticity, and malnutrition since birth. Died at age of 38 days. *26*, Spastic after weeks of fever following birth. Weighs 11 pounds at age of 2½ years.

A careful family history was obtained by interviewing available adult members of Family 1. The results of those interviews can best be shown by the genetic chart, Fig. 4.

Routine ophthalmoscopic examination was performed on M. J. O'C. who was being observed periodically. This patient showed a typical lipemia retinalis, so that other members of the family were subjected to routine funduscopic examination.

The characteristic picture of lipemia retinalis is produced when neutral fat in the blood stream rises above a certain level. Dunphy[2] observed that retinal vessels appeared normal at a blood fat concentration of 2,000 mg. per cent and became chylous at 2,500 mg. per cent. This is in accord with other investigators who report that lipemia retinalis appears when neutral fats in the blood serum are 2,500 mg. per cent or more. Lipemic changes have been noted in the retinal vessels at a concentration of 500 mg. per cent when neutral fat determinations are made on centrifuged blood specimens. Lipemia retinalis does not appear at a critical level and the range at which it disappears is usually lower than that at which it was first observed. Most instances of lipemia retinalis have been observed in diabetics; however, it has been seen in other diseases. The occurrence of lipemia retinalis could easily go undetected if a fundic examination was not made since changes in the neutral fat content of the blood do not usually affect vision.

No one in the course of numerous laboratory examinations had noticed a chylous appearance of the blood of any of the patients involved here. Blood specimens were obtained from members of the families (excepting the fathers) even though only one member of Family 1 (M. J. O'C.) was found to have lipemia retinalis. The collected blood samples were subjected to lipid partition studies.

Although samples of brain tissue which had been preserved in histological fixatives were also available, it was decided that use of these samples for analysis would be unwise[3] in spite of the remarks of Brante.[4] For this reason the data to be presented are based entirely on blood studies.

METHODS

All solvents were freshly redistilled; all other materials were reagent grade. Chemical analyses of the sera were conducted according to a scheme designed to permit the use of the smallest possible sample volume consistent with good results since it has been shown that separation of the blood lipids is to a certain extent a function of the sample volume employed.[5] The total lipids were extracted according to Boyd,[6] except that a sample to solvent ratio of 1:25 was used. Extraction with alcohol and ether was followed by rectification with petroleum ether, and all evaporations were carried out under reduced pressure in an atmosphere of carbon dioxide. The petroleum ether extracts were washed according to Christensen,[7] after which the total lipids were determined by weighing an evaporated aliquot of the extract. Other aliquots were analyzed for lipid P by Youngberg and Youngberg's[8] modification of the Fiske and Subbarow[9] procedure, and for cholesterol by the procedure of Schoenheimer and Sperry.[10] Total phospholipids were calculated as 25 times total lipid P. Neutral fat as such was not measured but was obtained by difference. This throws the burden of accumulating systematic error entirely on the values for neutral fats but it is not likely that the resulting figures are in error by more than the expected normal variation of the neutral fats.[11] Fractionation of the phospholipids was carried out essentially according to

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Hack,[12] the choline being measured by the Winzler and Meserve[13] modification of the Glick[14] analysis. Phospholipid turnover studies were conducted according to the procedure described by Cornatzer and Cayer.[15]

No attempt was made to measure steroids or degree of unsaturation of the blood lipids. A sample of the serum from this same patient was also treated according to the procedure described by Folch and Lees,[16] and while a small amount of "fluff" attributed by these authors to existence of proteolipids was present, the single experiment was too inconclusive to be worth more than passing mention.

ANALYTICAL RESULTS

Table II summarizes the results of our analyses for the blood lipid fractions. By comparison with the data of Table III it can be seen that with two exceptions the total serum lipids are within the normal bounds. The exceptions are found in Case 7 which represents a severe case of degenerative cerebral disease and Case 10 which was a sample of cord blood obtained at delivery. The latter sample not only had a low total lipid but each of the fractions measured was reduced proportionally (see Case 10, Table II). The low values are hard to explain in view of the fact that serum lipids usually rise in pregnancy, levels of about 900 mg. per cent not being uncommon at term.[17]

The total phospholipids were elevated in one known case of the disease and within normal limits in another.

TABLE II. PARTITION OF SERUM LIPIDS

		ALL VALUES GIVEN IN MG. PER CENT							
CASE	SUBJECT	TOTAL LIPIDS	TOTAL PHOSPHO-LIPIDS	LECITHIN	CEPHALIN	SPHINGO-MYELIN	TOTAL CHOLES-TEROL	FREE CHOLES-TEROL	ESTER CHOLES-TEROL
1.	M. F.	655	163	106	36	27	137	67	70
2.	A. F.	600	115	90	13	12	178	83	95
3.	C. F.	750	215	–	–	–	437	145	292
4.	N. F.	685	190	109	22	69	197	106	91
5.	M. R.	780	223	165	18	40	169	71	98
6.	V. T.	875	167	113	21	33	304	103	201
7.	M. O'C.	3,120	820	642	91	87	792	315	477
8.	J. A. O'C.	495	105	75	7	23	151	92	59
9.	A. O'C.	450	103	71	5	27	195	101	94
10.	A. O'C.*	345	75	52	4	19	158	105	53
11.	J. A. S.	643	183	122	11	50	228	165	63
12.	J. S.	602	273	190	20	63	261	139	122
13.	M. A. S.	730	275	168	34	73	178	101	77
14.	Jo. S.	460	293	214	31	48	129	67	63
15.	C. S.	560	343	235	37	71	183	104	79
16.	T. S.	475	140	109	4	27	218	96	122
17.	R. D.	520	155	103	27	25	212	83	129

*Repeated analysis at birth of J. A. O'C.

TABLE III. NORMAL VALUES FOR SERUM LIPIDS[19]

	ALL VALUES IN MG. PER CENT							
	TOTAL LIPIDS	TOTAL PHOSPHO-LIPIDS	LECITHIN	CEPHALIN	SPHINGO-MYELIN	TOTAL CHOLES-TEROL	FREE CHOLES-TEROL	ESTER CHOLES-TEROL
High	675	220	204	–	–	199	62	128
Mean	530	165	107	7	41	152	46	106
Low	385	110	50	–	–	105	30	75

However, at least two cases showed a definitely increased total phospholipid in the absence of any stigmas. All of the lecithin values were within normal expectations, again with the exception of the extreme hyperlipemia of case M. J. O'C. The small sample available in Case 3 precluded any breakdown of the phospholipid fractions. Cephalin levels were variable, and were suspiciously high in the siblings of the pathologically proved cases. The sphingomyelin figures also showed considerable variation, including several rather low values, but, in general, the siblings of Case 3 and Case 7 showed serum sphingomyelin levels higher than normal.

Total cholesterol was markedly elevated in both proved cases, and in several others were somewhat above the generally accepted limits, but the ratio of free to total cholesterol seemed to show no predictable pattern; in fact, there are several instances in which the usual ratio is reversed. For this we have no explanation.

The phospholipid turnover studies using P^{32} are graphically expressed in Fig. 5. Several interesting features of these experiments are notable. The curves for subjects M. J. O'C. and J. A. O'C. both show very steep gradients, although the first of these is clinically diseased while the second, apparently, is not. Subject B. W. was not a part of this series of cases, but was called to our attention because of a marked hyperlipemia (total serum lipids of 2,360 mg. per cent, serum phospholipids of 418 mg. per cent, total cholesterol of 1,085 mg. per cent)

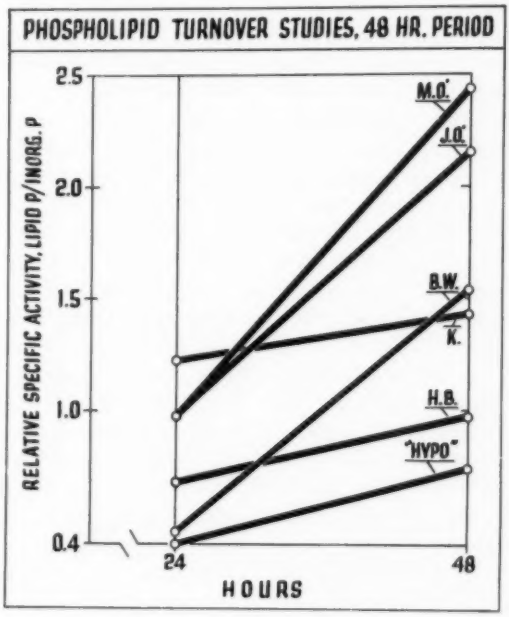

Fig. 5.

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with xanthoma planum of the skin and long-standing jaundice. She did not have clinical diabetes mellitus. Surgical biopsy yielded a diagnosis of biliary cirrhosis. In spite of the different association of the hyperlipemia the gradient of the turnover in this case is exactly the same as in patient J. A. O'C., but the absolute values are obviously lower. Curve H. B. was obtained from a known diabetic with marked hyperlipemia: in this case the gradient is low and comparable with that of the curve marked HYPO, which is a hypothetical curve constructed from the data of Cornatzer and Cayer. Curve K was obtained for further comparison from an infant 2 months old who was under routine nursery care. Although the absolute values of turnover are in all cases different, the curves K, H. B., and HYPO show a remarkable parallelism, indicating that the kinetics of phospholipid metabolism in these cases is normal. It is equally obvious that curves M. J. O'C. and A. J. O'C. describe a markedly accelerated rate of phospholipid turnover. The curves, however, do not reflect changes in individual phospholipid fractions.

DISCUSSION

Diffuse sclerosis of the brain has been discussed under a variety of names. Proper names and pathological terms are used to indicate an identical disorder. Krabbe's disease, Scholz's disease, and the Merzbacher-Pelizaeus syndrome refer to an identical pathological entity, with age of onset being the factor of differentiation within a group of demyelinating disorders having a familial quality. It is not possible on clinical grounds to utilize the characteristic of visual or mental deterioration in order to differentiate Krabbe's disease from the remainder of the group since death may occur at a relatively early age (in one of our patients at 42 days).

Krabbe[20] reported five cases of infantile cerebral degeneration in 1916. He referred to "a new form of diffuse brain sclerosis." The description of this author lists periodic attacks of screaming and muscular rigidity as prodromal symptoms. Periodic fever was the rule, and no complications could be found as the explanation of the febrility. He finally concluded that the fever was a characteristic of the disorder, either due to an effect on the central temperature control mechanism or to periodic destruction of nerve tissue. Vomiting and diarrhea were common symptoms and in four of his five patients the optic nerve was involved. Krabbe described the pathology well. He noted destruction of the axis cylinders and the axillary sheaths with replacement of the destroyed tissue by neuroglia with the nerve cells themselves remaining relatively intact. The pattern of progression involved the nerve cell processes of the cerebral and cerebellar cortex first, then the basal ganglia, and finally the spinal cord.

The fact remains that there is no knowledge concerning the pathogenesis of infantile cerebral degeneration of the heredofamilial type. We have evidence again as reported on frequent occasions that the process of demyelination in its heredofamilial form is carried by the asymptomatic carrier (maternal) and transmitted to the male in a sex-linked chain. The female can be affected but tends to suffer a less rampant course. Davison[21] has reviewed the theories of etiology with

particular reference to multiple sclerosis, but the same thoughts are involved in the general group of demyelinating disorders. It is as obvious now as it was to the early writers that the theory of infection can be ignored. One theory has been advanced which bases the degeneration on a toxic lipase acting to destroy myelin. Some observers believe that the liver acts as the seat of production of this agent, or that the liver has lost its power to destroy such an agent.

The constitutional theory holds that the primary lesion is in the subcortical oligodendroglial cells with secondary derangement of myelin metabolism. It is pointed out that the nutrition of the myelin sheath and axis cylinders depends upon the functional integrity of the oligodendroglial cells. It is stated that the products of deterioration of the myelin disturbance takes other forms than that noted (neutral facts) in the compound granular corpuscles in wallerian degeneration. A number of investigators refer to these products of degeneration as prelipoids, which are closely allied to the lipids found in the nerve cell in Tay-Sachs and Niemann-Pick disease.

A correlation seems to exist between the pathological evidence from brain sections and aberrations noted in the serum lipid partition. The demyelinating process of Krabbe's disease is associated with elevated serum cholesterol and serum sphingomyelin levels, and the same may be true for serum cephalin levels. The underlying link between the loss of the lipids from the central nervous system on the one hand and the increased serum lipid content on the other is still an unsolved matter. Apparently an individual of a given genetic structure may carry the *tendency* toward hyperlipemia involving the specific phosphatides mentioned above without being, necessarily, clinically afflicted with the disease. It is also true that the onse of definable disease may occur at different periods in life, so that the characteristic symptoms must be triggered by a sudden failure of an enzymatic link of great urgency in lipid metabolism; the genetic failure may involve a matter of degree.

While the blood lipid content is more or less constant in health, the lipid content of the brain is markedly different in the infant or child as compared to the adult. Table IV from the data of Johnson and associates[22] gives the details of the observed changes. Also, the brain is not of uniform structure with respect to lipid content, and aside from the differences between white and gray matter, there are important variations from one area of the brain to another. Table V from the studies of Randall[18] emphasizes this important fact. The lipids may occur in the "free" state, as liponucleoproteins,[23] as proteolipids,[15] and as the classical lipoproteins. It has also been demonstrated by Chaikoff and his collaborators[24, 25] that incorporation of P^{32} into brain lipids occurs at different rates, depending on the lipid and the area of the brain studied.

It is generally stated that the role of brain lipids must be structural or physical; the cited evidence is based on an R.Q. of 1.0 in perfusion studies, indicating consumption of carbohydrate only. Most early studies of surviving slices gave rise to the same conclusions, but recently Geyer and coworkers[26] have shown that brain tissue will oxidize octanoic acid in low concentration (0.003 M) at a rate

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equal to or greater than the rate for liver slices. Brain slices were also capable of considerable oxidation of trilaurin. These observations do not mean that brain in vivo must metabolize lipids, or even that it will, but the capacity to do so in vitro cannot be ignored. Volk and associates[27] have also found high activity of isotopic phosphorous incorporated in an acetone-soluble lipid fraction which may be of great metabolic significance in brain and in other tissues as well. This fraction was apparently not in equilibrium with the bulk of tissue lipids under their experimental conditions. Sperry[28] has confirmed the synthetic capacity of the brain in vitro, using a perfusion technique with added carboxyl-labeled octanoate. He found that a significant quantity of the label appeared in two phospholipid fractions. Labeled pyruvamide led to substantially the same conclusions.

TABLE IV. LIPID COMPOSITION OF THE BRAIN

COMPONENT	GRAY MATTER			WHITE MATTER		
	INFANT	ADULT	ADULT / INFANT	INFANT	ADULT	ADULT / INFANT
	Expressed as per cent wet tissue weight					
Cerebroside	0.52	0.87	1.67	0.58	4.78	8.25
T. cholesterol	0.49	0.99	2.02	0.67	4.22	6.30
F. cholesterol	0.48	0.97	1.98	0.64	4.15	6.50
E. cholesterol	0.01	0.02	–	0.03	0.07	–
Phospholipids	1.77	2.83	1.60	1.96	5.03	2.57
Lecithin	0.75	0.99	1.32	0.85	1.37	1.61
Cephalin	1.02	1.85	1.81	1.11	3.66	3.30
Sphingomyelin	0.12	0.53	4.42	0.13	2.00	15.40
Water*	9.74	5.34	0.55	9.82	2.40	0.25
	Expressed as per cent dry tissue weight					
Cerebroside	5.54	5.54	1.00	6.21	16.28	2.61
T. cholesterol	5.09	6.28	1.23	7.00	14.33	2.04
F. cholesterol	5.03	6.17	1.23	6.70	14.08	2.10
E. cholesterol	0.06	0.10	–	0.30	0.26	–
Phospholipids	19.56	21.27	1.08	22.04	23.84	1.08
Lecithin	7.81	6.25	0.80	1.40	6.82	4.87
Cephalin	10.46	11.71	1.11	11.57	12.39	1.07
Sphingomyelin	1.30	3.03	2.33	1.40	6.82	4.87

*All values for water expressed as mg./mg. dry tissue weight.

TABLE V. DISTRIBUTION OF BRAIN LIPIDS*

COMPONENT	AS PERCENTAGE OF DRY WEIGHT						
	CORONA RADIATA	FRONTAL WHITE	FRONTAL CORTEX	PARIETAL WHITE	PARIETAL CORTEX	BRAIN STEM	CAUDATE NUCLEUS
Water†	69.83	70.64	84.12	69.92	81.15	71.67	75.79
Total lipid	57.30	55.37	31.98	57.18	32.77	54.21	33.46
T. cholesterol	15.15	14.23	5.98	14.79	6.23	13.51	6.65
F. cholesterol	14.37	13.62	6.16	14.34	6.36	13.17	6.58
Phospholipids	40.33	38.54	24.17	40.86	24.71	38.59	24.12
Lipid P × 25	30.80	29.79	25.24	29.90	25.15	30.42	25.95
Inorg. P	0.16	0.16	0.24	0.15	0.24	0.20	–
Lipid N	1.04	1.05	0.92	1.11	0.97	1.04	–
Iodine number	84	84	129	84	129	88	116

*In order to have enough material to obtain reliable values some of the brains in this series were from psychotic individuals; although there is a possibility that the composition of these might differ from the normal there is no present evidence that this is so.

†Percentage of water based on wet tissue weight.

These data were obtained from short-term experiments, from seventeen- to thirty-two-minute duration, and furnish an excellent indication of the rapidity of the synthetic process.

Phospholipids which are usually considered as cytoplasmic or structural substances may under certain circumstances assume the role of "lipometabolic phospholipids."[29, 30] Waelsch and collaborators[31] have calculated that about 20 per cent of the brain fatty acids are turned over per week, a rate some 300-fold less than the activity of the liver, but these studies do not take into account possible localized rates in excess of the observed values, rates more nearly akin to those of liver and muscle. Moreover, they do not take into account differences in the rates for various lipid substances. The work of Chargaff and associates[32] is very important in this connection, as it demonstrates that cephalin and sphingomyelin portions of brain lipids are renewed more rapidly than brain lecithin. Table II showed that cephalin and sphingomyelin were the phosphotidic entities specifically affected in Krabbe's disease. Kennedy and Lehninger[33] have shown that fatty acid oxidation occurs almost exclusively in or on the mitochondria and microsomes, and it is also true that these same elements contain the bulk of the cellular lipids.[34] It is unlikely that the mitochondria would undergo self-catabolism provided an adequate supply of substrate was available for other sources at a rate and in a manner suitable for cellular purposes.

Returning to the link between the brain lipid loss and the blood lipid increase we may entertain several possibilities: (1) failure of the blood to deliver essential substrates to the cerebral cells at an adequate rate in an adequate mixture, (2) a proper functioning of the blood with an inadequate uptake of the substrate by the cerebral cells; (3) failure of the mitochondria or microsomes to fabricate the lipid molecules from the substrates, and (4) the inability of the cerebral cells to hold prefabricated lipid molecules in the normal organizational pattern, with subsequent loss of the lipid substances to the blood across the *brain-blood* barrier, which may well be very different from the *blood-brain* barrier.

The first possibility cannot be completely ignored, but there are no known nutritional factors involved, and no other systemic signs of lipodystrophy were observed. Certainly a wide variety of substances are available as substrates. The second possibility is also unlikely (and further helps to rule out the first) chiefly on the evidence of scarring where lipid was once laid down and also on the evidence of the elevated blood lipids. The third possibility is even more unlikely, since the mitochondria are responsible for processes other than lipid metabolism, and it is unlikely that such mitochondrial disturbances could be very extensive in space or time before death intervened. Yet we have, in this series of cases, one example of survival time measured in years. Furthermore, this supposition would not explain the blood lipid findings. The fourth alternative is an attractive hypothesis, especially since Fishler and co-workers[35] have shown that the normal source of the blood lipids is the liver. In dogs receiving P^{32} as a labeling agent the specific activity of the plasma lipids was exceeded only by

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those of the liver; hepatectomized dogs produced small amounts of labeled lipids in the gut and the kidney, but with negligible release of these to the blood. If the brain does synthesize and destroy lipids throughout life then it is entirely possible that the demyelinating process involves primarily a disproportion between build-up and breakdown in the brain itself, without regard to other tissues or transport mechanisms. Interference with some process, not necessarily associated with lipid metabolism per se, might permit loss of an essential component, or as it appears here, of total lipid molecules themselves. The high turnover rate of serum lipids which we have observed lends some credence to this possibility, provided one assumes that the data reflect cerebral activity and not hepatic activity. This assumption seems justified since hepatic involvement was not present in our study. In the presence of the lipid loss occasioned by the demyelinating process, the brain marshalls its synthetic powers in a desperate effort to maintain a semblance of normalcy. The fact that it does not succeed in no way detracts from the possibility that such a mechanism exists.

It should be noted in conclusion that the biochemical changes described have not been of help in the differentiation between Dr. Meyer's patients and our own from the standpoint of premortem diagnosis. Our patients are best grouped under the heading of Krabbe's disease. The gray matter involvement described neuropathologically in Dr. Meyer's patients would make it reasonable to classify them under the heading of Alper's disease. Certain features noted may make revision of this diagnosis necessary at a later date.

The abnormalities in lipid metabolism as shown (Table II) are clear cut. Case 11 is a 5-year-old boy who shows only an elevated cholesterol level. Cases 12, 13, and 15 are girls ranging in age from 2½ to 7 years. These children have high blood phosphatides, especially sphingomyelin. The total cholesterol was elevated in the diseased patients and in some of the siblings as well. This may be of no clinical significance, yet it gives a startling suggestion that the carrier state exists.

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PHTHALYLSULFATHIAZOLE (SULFATHALIDINE) IN THE TREATMENT OF ENTEROBIASIS (PINWORM INFECTION)

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WITH THE TECHNICAL ASSISTANCE OF VERA DROUGHMAN**

UNTIL recently there has been no laboratory method for selecting compounds for the treatment of human enterobiasis. The parasites will not survive outside the host for long periods, and they cannot be transmitted to laboratory animals.[1] In testing therapeutic agents against two species of mouse pinworm, *Aspicularis tetraptera* and *Syphacia obvelata*, Wells[2, 3, 4] and Chan[5] obtained results of clinical significance. Despite species differences in both host and parasites their studies indicated anthelmintic effects with gentian violet, phenothiazine, oxytetracycline (Terramycin), and bacitracin comparable to those observed in human enterobiasis.

Because Chan's work demonstrated that Sulfathalidine† significantly decreased the number of *Syphacia obvelata* in mice, studies in man with this sulfonamide were undertaken Previous work by Sisk[6] indicated that although this compound, as well as others of the group of poorly absorbed sulfonamides, had anthelmintic activity, they did not completely eliminate *Enterobius vermicularis* in a significant number of patients.

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**Children's Heart Hospital of Philadelphia, Pa.

†Sharp and Dohme's trademark for this drug which has the generic designation "phthalylsulfathiazole." Both Sulfathalidine tablets and a suspension known as Cremothalidine were supplied for this study by the manufacturer.

MATERIALS AND METHODS

Studies were carried out in two institutions, the Children's Heart Hospital and St. Christopher's Hospital for Children. The techniques for the diagnosis of enterobiasis previously described[7] were adapted to the available technical personnel and the character of the patient population.

*Hospitalized Patients.**—The children treated ranged from 4 to 12 years of age. Almost all of them were in the convalescent phase of acute rheumatic fever and were ambulatory. Scotch Tape swabs were obtained by the nursing staff each morning for seven consecutive days from all patients prior to their arising.

The swabs were examined by one of us shortly after their completion. In consultation with the medical director, a decision was then made as to the management of each infected child. Anthelmintic therapy was postponed for children suspected of having active rheumatic fever, because of the possible deleterious effect of sulfonamides on this disease. If eligible for treatment at a later date, these children were re-examined to see if they still harbored helminths. Gentian violet was used for the treatment of individuals suspected of sensitivity to any of the sulfonamide drugs. In patients in whom Sulfathalidine was not contraindicated, therapy with this

*Children's Heart Hospital.

compound was started within a few days of completion of the survey. Treatment was given for one or two weeks. Then after a week of no diagnostic or therapeutic measures, from seven to fourteen post-treatment Scotch Tape swabs were made. As in an earlier study[7] no patient was classified as cured unless he had at least seven negative consecutive post-treatment swabs.

*Ambulatory Clinic Patients.**—Parents seeking help for their children infected with pinworms were referred to one of us in the Medical Clinic. Each mother was taught how to make Scotch Tape swabs and was instructed to make an early morning swab for three consecutive days on each member of the family. On returning the swabs to the clinic, the mothers were given sufficient Sulfathalidine for the prescribed course of treatment and written direction for its administration to all members of the family. Sulfathalidine was not employed for those with a previous history of sensitivity to any medication. In the outpatient group, swabs were made from the eighth through the fourteenth day of the post-treatment phase.

After preliminary experiences indicated that infants and small children had difficulty swallowing Sulfathalidine tablets, a stable and palatable suspension of the drug (Cremothalidine) was employed throughout the rest of the study. When one therapeutic trial failed, the patient was retreated, employing the same or another dosage schedule.

Doses employed were within the ranges recommended by the manufacturer and *New and Nonofficial Remedies*.[8] They were:

*St. Christopher's Hospital for Children.

Sulfathalidine: 0.5 to 4.5 Gm. a day for 7 days.

Under 4 yr.	1 to 2 tab. daily (0.5-1.0 Gm.)
4 to 6 yr.	1 tab. t.i.d. (1.5 Gm.)
6 to 8 yr.	2 tab. b.i.d. (2.0 Gm.)
8 to 13 yr.	2 tab. t.i.d. (3.0 Gm.)
Over 13 yr.	3 tab. t.i.d. (4.5 Gm.)

Sulfathalidine: 2.0 to 6.0 Gm. a day for 7 days.

Under 4 yr.	2 tab. b.i.d. (2.0 Gm.)
4 to 6 yr.	3 tab. b.i.d. (3.0 Gm.)
6 to 8 yr.	4 tab. b.i.d. (4.0 Gm.)
8 to 13 yr.	5 tab. b.i.d. (5.0 Gm.)
Over 13 yr.	4 tab. t.i.d. (6.0 Gm.)

Cremothalidine: 2.0 to 6.0 Gm. a day for 7 or 14 days.

Under 4 yr.	1 tsp. b.i.d. (2.0 Gm.)
4 to 6 yr.	1½ tsp. b.i.d. (3.0 Gm.)
7 to 9 yr.	2 tsp. b.i.d. (4.0 Gm.)
10 to 13 yr.	2½ tsp. b.i.d. (5.0 Gm.)
Over 13 yr.	3 tsp. b.i.d. (6.0 Gm.)

Cremothalidine: 1.0 to 8.0 Gm. a day for 7 days.

Under 1 yr.	½ tsp. b.i.d. (1.0 Gm.)
1 to 4 yr.	1 tsp. b.i.d. (2.0 Gm.)
4 to 6 yr.	2 tsp. b.i.d. (4.0 Gm.)
7 to 9 yr.	2½ tsp. b.i.d. (5.0 Gm.)
10 to 13 yr.	3 tsp. b.i.d. (6.0 Gm.)
Over 13 yr.	4 tsp. b.i.d. (8.0 Gm.)

Gentian violet was administered in the form of four-hour enteric-coated tablets in divided doses after meals. The doses were the same as those previously tried.[7]

Gentian violet: 0.02 to 0.18 Gm. a day for 7 days.

Under 4 yr.	1 or 2 small tab. (0.02 Gm.)
4 to 6 yr.	3 small tab. (0.03 Gm.)
6 to 8 yr.	6 small tab. (0.06 Gm.)
8 to 13 yr.	3 large tab. (0.09 Gm.)
Over 13 yr.	6 large tab. (0.18 Gm.)

RESULTS

Children's Heart Hospital.—Because of possible rheumatic fever in several children and later because of an epidemic of mumps, treatment was deferred in eight infected children. Of these, three had at least seven negative swabs after a period of hypothetical "treatment."

Gentian violet was very effective, apparently ridding six children of worms without any therapeutic failures, even though three of this group vomited repeatedly during the course of therapy.

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Small doses of Sufathalidine, 0.5 to 4.5 Gm. a day, produced poor results with only two cures in a group of seven children. No toxic reactions were observed.

Trials with daily doses of 2 to 6 Gm. of Cremothalidine for fourteen days were more effective, curing twenty-three of twenty-nine children. This result was significantly better than in the control groups. On the tenth day of treatment one child had six of sixteen patients without any untoward reactions.

Two to 6 Gm. a day for one week cured five of eleven persons with two possible instances of toxicity. During very hot weather the mother of a large family reported that two children had subaxillary rashes. These children unfortunately were not seen by a physician at the time and it was not determined whether the rashes

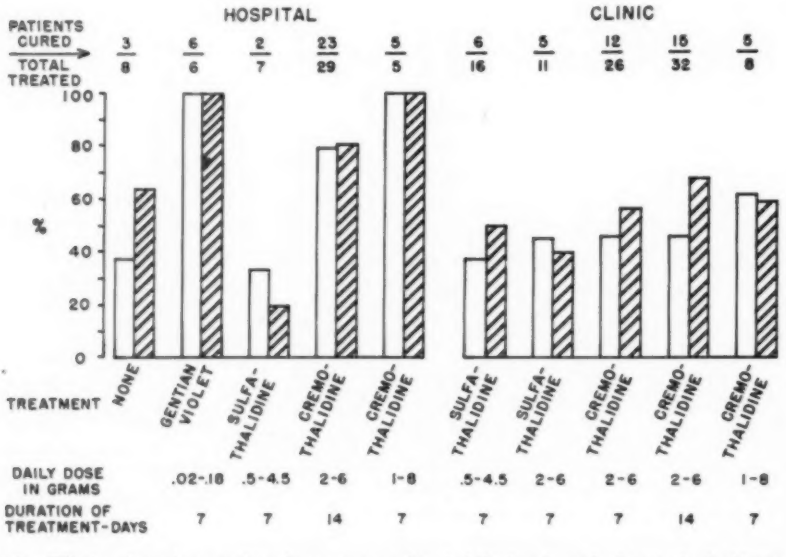

Fig. 1.—Effects of various regiments on cure rates (white bars) and change in incidence of ova-bearing slides (shaded bars).

urticaria which subsided promptly on cessation of therapy.

All of the five children treated for one week with 1 to 8 Gm. of Cremothalidine a day were cured without any evidence of toxicity. In comparison with the outcome of infection in the untreated group, this result is probably significant.

St. Christopher's Hospital for Children.—Sulfathalidine in daily doses of 0.5 to 4.5 Gm. for seven days cured represented miliaria or reactions to the medication.

Cremothalidine in daily doses of 2 to 6 Gm. was given for one week. Of twenty-six patients so treated, twelve were cured. When the same doses were administered for two weeks the results were no better, there being fifteen cures on thirty-two therapeutic trials. With a daily dose of 1 to 8 Gm. a day for one week

five out of eight persons were cured.

In hospital and clinic studies the incidence of ova-bearing slides was reduced after treatment (see Table I and Fig. 1).

DISCUSSION

Since apparent spontaneous cases can occur, the observation of an untreated group is advisable to prevent unwarranted enthusiasm about the anthelminthic potency of any drug.

Our primary responsibility in both institutions was the eradication of the parasites and we felt justified in withholding treatment in only eight hospitalized children because of definite contraindications. In keeping with the criteria established for successful therapy, three of them became spontaneously "cured" after a period of hypothetical treatment. On one child's seven "pretreatment" slides

TABLE I. THERAPEUTIC EFFECTIVENESS AND TOXICITY OF GENTIAN VIOLET, SULFATHALIDINE, AND CREMOTHALIDINE

TREATMENT	NO. PATIENTS	NO. CURED	TOXICITY	SCOTCH TAPE SLIDES		
				PRETREATMENT POSITIVE/ TOTAL	POST-TREATMENT POSITIVE/ TOTAL	DECREASE PER CENT POSITIVE SLIDES
			Hospital			
None	8	3 (38%)	–	20/56 (36%)	10/77 (13%)	64
Gentian violet 0.02-0.18 Gm. a day for 7 days	6	6 (100%)	3 patients vomited	14/42 (33%)	0/64	100
Sulfathalidine 0.5-4.5 Gm. a day for 7 days	7	2 (29%)	0	22/49 (45%)	35/98 (36%)	20
Cremothalidine 2-6 Gm. a day for 14 days	29	23 (79%)	1 patient had urticaria	132/229 (58%)	22/209 (11%)	81
Cremothalidine 1-8 Gm. a day for 7 days	5	5 (100%)	0	13/35 (37%)	0/35	100
			Clinic			
Sulfathalidine 0.5-4.5 Gm. a day for 7 days	16	6 (38%)	0	43/58 (74%)	42/115 (37%)	50
Sulfathalidine 2-6 Gm. a day for 7 days	11	5 (45%)	2 patients had rashes	20/48 (42%)	19/77 (25%)	40
Cremothalidine 2-6 Gm. a day for 7 days	26	12 (46%)	0	57/88 (65%)	51/182 (28%)	57
Cremothalidine 2-6 Gm. a day for 14 days	32	15 (47%)	0	88/116 (76%)	57/233 (24%)	68
Cremothalidine 1-8 Gm. a day for 7 days	8	5 (63%)	1 patient had abdominal cramps	26/30 (87%)	25/70 (36%)	59

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only one egg was found, another had ova on only one slide, but the third had four positive slides.

According to Jung and Beaver,[9] a low incidence of pretreatment positive slides is related to a high cure rate. This might account for the apparently better results in the hospital group where more children with a low incidence of ova-bearing slides were treated (see Table II). The number of patients in each group were too small for verification by statistical analysis.

negligible systemic toxicity. That this compound largely remains in the gastrointestinal tract is ideal for the treatment of enterobiasis, since the parasite's habitat is limited to the cecum, appendix, and colon.

Since infection with pinworms is a family problem, making treatment of all members of the family advisable, and since enterbiasis does not threaten life and frequently produces no symptoms, the use of expensive medication is rarely justified. Certain antibiotics such as oxytetracycline (Terramycin)[10] and bacitracin[11] are clinically effective but the necessity of treating family groups demands the consideration of economic aspects of therapy. Synergism between antibiotics and poorly absorbed sulfonamides demonstrated in mice by Chan[3] suggests that Cremothalidine in combination with an antibiotic by reducing the amount of antibiotic required may result in an effective and less expensive medication.

TABLE II. EFFECTS OF THERAPY ON PATIENTS WITH VARYING INCIDENCE OF PRETREATMENT OVA-BEARING SLIDES
CREMOTHALIDINE, 2 TO 6 GM. DAILY FOR FOURTEEN DAYS

HOSPITAL			CLINIC		
INCIDENCE OF OVA-BEARING SLIDES BEFORE TREATMENT* (%)	NUMBER OF PATIENTS	NUMBER CURED	INCIDENCE OF OVA-BEARING SLIDES BEFORE TREATMENT† (%)	NUMBER OF PATIENTS	NUMBER CURED
100	6	2 (33%)	100	10	3 (30%)
86	3	3 (100%)	75	1	0
71	4	4 (100%)	67	4	2 (50%)
57	3	2 (67%)	57	1	0
36	2	2 (100%)	50	2	1 (50%)
29	4	3 (75%)	33	7	6 (86%)
25	1	1 (100%)	14	1	0
14	5	5 (100%)			

*Only patients with at least seven pretreatment slides are included.
†Only patients with at least three pretreatment slides are included.

Although Cremothalidine is a weaker anthelminthic than gentian violet, nurses and mothers agreed that Cremothalidine was much easier to administer to infants and small children who had difficulty in swallowing enteric-coated gentian violet tablets. Those who had had previous experience with the gastrointestinal irritation and the vomiting of purple material from the use of gentian violet appreciated the lack of such reactions accompanying treatment with Cremothalidine.

The poor absorption of Sulfathalidine from the gastrointestinal tract accounts in large measure for the

CONCLUSIONS

1. Daily doses of Cremothalidine from 2 to 6 Gm. given for two weeks cured twenty-three (79 per cent) of

twenty-nine children in a children's hospital, and fifteen (47 per cent) of thirty-two in a clinic population of all ages. One to 8 Gm. a day given for one week cured all five children in the hospital group, and five of eight (63 per cent) in the dispensary.

2. Although not as potent an anthelmintic as gentian violet, Cremothalidine did not produce the gastrointestinal irritation associated with the dye, and because of its palatable liquid form was much easier to administer to infants and small children.

Note: Since the preparation of this paper, tablets each containing 0.2 Gm. of neomycin and 0.3 Gm. of Sulfathalidine have been tried. Three to ten tablets given twice a day for seven days cured nine children with no treatment failures. Because fifteen of twenty-three individuals treated complained of anorexia, nausea, or vomiting, the effectiveness of smaller doses should be studied.

Grateful acknowledgment is made to Dr. Ella Roberts, Medical Director of Children's Heart Hospital, and to Dr. John Bartram, Associate Professor of Pediatrics at Temple University, School of Medicine, for their encouragement and advice. We also thank the nursing staff at the Children's Heart Hospital who made the swabs at that institution.

The statistical analysis of these studies was done by Mr. Joseph L. Ciminera, Biometrician, Research Division, Sharp & Dohme Division, Merck & Co., Inc., West Point, Pa.

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THE TREATMENT OF PINWORM INFECTION (ENTEROBIASIS)

A Comparative Study of Three Oxyuricides

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IN THE past two years we have examined 1,768 patients in the wards and the clinics of the E. J. Meyer Memorial Hospital in Buffalo, N. Y., for pinworm infection. Of this number, 1,737 were children and thirty-one were adults. Using a modification of the Graham Scotch Tape swab technique, which we have minutely described in our published reports, we found that 523 or 30 per cent of the 1,768 patients were infected. Of the 523 infected, 513 or 98 per cent were children and ten or 2 per cent were adults.

In our search for an ideal oxyuricide, one that is easy to take, well tolerated and inexpensive, we have to date evaluated these nine drugs: Egressin, Diphenan, gentian violet, Terramycin, papain, Cremothalidine, Magnamycin, garlic, and piperazine. The results obtained with five of these have been published. Papain[1] was effective in 10 per cent of thirty cases, Egressin[2] in 54 per cent of thirty-nine cases, Diphenan in 30 per cent of forty cases, gentian violet in 84 per cent of thirty-eight cases, and Terramycin in 85 per cent of thirty-nine patients treated.[3] Gentian violet and Terramycin, the most effective of these oxyuricides, were not completely satisfactory. The younger children were not able to swallow the intact enteric-coated gentian violet tablets, and in some patients it caused nausea and vomiting, with abdominal cramps. The cost of Terramycin and the possibility of establishing sensitivity to an important antibiotic are decided drawbacks in treating pinworm infections with this drug. The percentages of cures obtained with Egressin, Diphenan, papain, Cremothalidine, and Magnamycin were sufficiently low to make them of questionable value.

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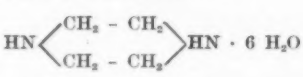
CLINICAL MATERIAL AND METHOD

One hundred and fifty-five children infected with pinworms were treated with one of three oxyuricides. All of these children, ranging in age from 2½ to 16 years, were residents of the German Roman Catholic Orphanage in Buffalo, N. Y. Forty-seven of these infected children were treated with piperazine hexahydrate, fifty were treated with Terramycin, and fifty-eight with dehydrated garlic powder. Each treatment group contained an almost equal number of children from 1 to 5 years, 6 to 10 years and 11 to 16 years of age. The diagnosis in all cases was established by the use of a modification of the Graham Scotch Tape swab technique which we have described in detail in earlier publications. In this study, we used a new Scotch Tape which is more transparent, with a crystal-clear

adhesive that makes the identification of the pinworm eggs much easier. This tape is designated as Scotch acetate film tape No. 800. Seven days after treatment, Scotch Tape swab smears were made daily for one week to determine the results of the treatment. Those patients who had seven consecutive negative smears were declared cured. The remaining eighty-one children of the orphanage had negative diagnostic Scotch Tape smears. These children, even though they were considered free of pinworm infection, were also treated with either Terramycin or garlic. Fifty were treated with Terramycin and fifty-eight with garlic. By treating the entire pediatric population of the orphanage we hoped to minimize the possibility of allowing infected children who had negative diagnostic smears to go untreated and possibly reinfect the treated cases. The adult population of the orphanage was not treated since none of them presented symptoms that suggested pinworm infection.

Piperazine hexahydrate, a white crystalline substance, has the following structural formula:



It is readily soluble in water to give a clear colorless alkaline solution. It is not hygroscopic and is stable in solid form. Piperazine has been used for many years in the treatment of gout and urinary calculi. It produces no symptoms and is practically nontoxic.[4] The acute and chronic toxicity tests of piperazine conducted by the Wellcome Research Laboratories have established its nontoxicity in the normal dosage range.

Mouriquand and associates[5] treated mice infected with *Aspicularis tetraptera* and Syphacea with piperazine hexahydrate and reported satisfactory anthelminthic properties toward these mouse oxyurids. They also treated a group of children ranging in age from 3 to 15 years with a high proportion of cures and reported that piperazine was "easily accepted by children and very well tolerated even by the very small." Standen[6] has also successfully treated *Aspiculuris tetraptera* with piperazine and recommended that it be used in the treatment of human pinworm infection. White and Standen[7] treated a group of thirty-one children with piperazine hexahydrate syrup at a dose level of 50 to 75 mg. per kilogram per day with a 97 per cent cure rate. They also reported no toxic effects in dose levels as high as 150 mg. per kilogram daily and found that piperazine was extremely well tolerated by all but one of the thirty-one children treated. Brown[8] in this country has also found piperazine quite effective against the mouse pinworm, *Aspiculuris tetraptera*. So far as we can determine, there are no reported series of cases of enterobiasis treated with piperazine in this country.

Forty-seven of the infected children were treated with a palatable 10 per cent syrup containing 100 mg. of piperazine hexahydrate per cubic centimeter. Without any previous preparation these patients were treated for seven days, rested for seven days, and then treated for seven more days. After a lapse of seven days, following the last day of treatment, one Scotch Tape swab smear was taken daily, early in the morning, before the patients were bathed, to determine the

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results of the treatment. In addition to the piperazine hexahydrate syrup treatment, the usually recommended personal and environmental hygienic measures were adhered to as closely as possible. This same routine was followed in treating the children with Terramycin and garlic. Table I lists the number of cases treated with these three oxyuricides, the dosage used, the duration of treatment, and the result of treatment.

For many years raw garlic has been used in many parts of the world as a "popular remedy" for pinworm infection. Many clinicians consider raw garlic as one of the best oxyuricides. Eckerle[9] in his study (personal communication) used raw garlic, one clove every other night for fourteen days, interrupted by a one-week rest period. He recommends raw garlic mixed with grated carrots and mayonnaise, served in a sandwich. Fresh parsley eaten immediately after the garlic sandwich acts as a natural deodorizer. Vanni[10] also reported deodorized garlic tablets as the treatment of choice for enterobiasis. Killingsworth and associates[11] used raw garlic in the treatment of pinworm infection with 87 per cent cures.

In our study, fifty-eight of the infected children at the German Roman Catholic Orphanage were treated with a mint-flavored syrup containing 8 grains of dehydrated garlic powder* to the teaspoonful. In addition to the garlic treatment, the usually recommended personal and environmental hygienic measures were carried out as best as possible. Table I indicates the number of cases treated, dosage, and per cent of cures with the garlic syrup. The garlic syrup was very well accepted and tolerated by all the children and no untoward effects were noted in all fifty-eight children treated.

In a recent study[3] on the treatment of enterobiasis with Terramycin we reported a cure rate of 85 per cent of forty infected children treated with 10 mg. of Terramycin per pound of body weight, divided into three daily doses for a period of seven days. Loughlin and co-workers[12] treated thirty patients with enterobiasis with 1 to 2 Gm. of Terramycin base for five days with a 100 per cent cure rate. In this study we treated fifty of the infected children at the German Roman Catholic Orphanage with 5 mg. of Terramycin† per pound of body weight, divided into three daily doses for a period of fourteen days with a seven-day rest period at the end of the first week of treatment.

TABLE I

DRUG	CASES	DOSAGE	DURATION	% CURED
Piperazine hexahydrate	47	1-5 yr. ½ tsp. t.i.d. 5-10 yr. 1 tsp. t.i.d. 10 yr. and up, 1½ tsp. t.i.d.	7 days treatment 7 days rest 7 days treatment	85
Garlic syrup	58	1-10 yr. 1 tsp. t.i.d. 10 yr. and up, 2 tsp. t.i.d.	7 days treatment 7 days rest 7 days treatment	7
Terramycin	50	5 mg. per pound of body weight divided into 3 daily doses	7 days treatment 7 days rest 7 days treatment	38

*Garlic powder as a mint-flavored syrup was supplied by the Van Patten Pharmaceutical Co.

†Terramycin was supplied by the Chas. Pfizer & Co., Inc.

The same precautions and routines were used in the treatment of this group of patients that were used with the piperazine and garlic treatment. The same rigid measure of cure, seven consecutive negative Scotch Tape smears taken seven days after the termination of the treatment, was also carried out. The percentage of cures obtained with the decreased dose of Terramycin is indicated in Table I.

RESULTS AND DISCUSSION

Of the forty-seven patients treated with piperazine hexahydrate, forty had seven consecutive negative post-treatment Scotch Tape smears, the remaining seven patients had one to seven positive post-treatment smears. The cure rate in this series of patients treated with piperazine hexahydrate was 85 per cent.

All the patients in this series took the palatable syrup of piperazine readily and tolerated it very well. Sample post-treatment blood counts done on ten of the patients were normal, and sample post-treatment urinalyses done on twenty of the patients were negative, except for three female children who showed evidence of cystitis which we believe was not caused by, nor related to, the piperazine treatment.

Even though the percentage of cures obtained in the group of fifty-eight patients treated with garlic was only 7 per cent, we are of the opinion that garlic should not be discarded as an oxyuricide. Two errors made in our garlic study might have, at least in part, contributed to this low percentage of cures. The 8 grains of dehydrated garlic, given three times daily, making a total daily dose of 24 grains of dehydrated powder, could have been an inadequate dose. Since most of the studies on the garlic treatment of enterobiasis used one "pod" or "clove" of garlic, we weighed many "cloves" of garlic to arrive at an average weight of a clove of garlic. After weighing many cloves of garlic that were obtained in local food shops, we concluded that the average weight of a clove was 11 grains. We prepared a mint-flavored syrup containing approximately 8 grains of dehydrated garlic powder to the teaspoon. This was the syrup we used in treating fifty-eight of the infected children at the German Roman Catholic Orphanage. At the conclusion of the study we learned that garlic cloves most usually available through food shops average 46 grains. This information has been confirmed by the U.S. Department of Agriculture.* Since the completion of this study, we again obtained samples of garlic cloves from local food shops and found that the average weight of these cloves was 60 grains. However, the replacement ratio between raw and dehydrated garlic is 1 to 6, on the average, one part of dehydrated garlic equals six parts of raw garlic. On this basis, even with the error made in computing the average weight of a clove of garlic, the dosage used in our study could well have been an adequate dose. The possibility that some active principle of garlic is lost in the dehydration process should also be considered in evaluating the garlic treatment of enterobiasis. The second error which we feel we should explain is that the bottles containing the garlic syrup were not carefully shaken be-

*Leaflet No. 138, entitled *Production of Garlic.*

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fore a dose was administered and for this reason the individual doses of garlic syrup could have varied considerably. How much this error contributed to the low percentage of cures in the garlic group we are not able to state with any degree of accuracy.

Of the fifty patients treated with the reduced dose of Terramycin, 5 mg. per pound of body weight, only 38 per cent had seven consecutive negative post-treatment Scotch Tape smears. This percentage of cures is less than one-half the percentage of cures obtained in our earlier study in which we used 10 mg. of Terramycin per pound of body weight. This study suggests that the 5 mg. per pound of body weight dose is not adequate to produce the direct deleterious action upon the mature gravid female worms and on the fertilized eggs as suggested by Loughlin and associates.[12]

SUMMARY

1. The percentage of cures with piperazine, 85 per cent, obtained in this series of forty-seven patients compares very favorably with the cures obtained with Terramycin and gentian violet. Since the syrup of piperazine used in this study was easy to take, well tolerated, and, we are assured, can be made available inexpensively, we are of the opinion that of the nine oxyuricides that we have tested to date, piperazine hexahydrate* comes the closest to our standard of an ideal oxyuricide.

2. We have been able to confirm the study of White and Standen, as reported in the English literature, that piperazine hexahydrate is a nontoxic, safe, and effective oxyuricide.

3. The 7 per cent cures obtained with dehydrated garlic powder in this series of fifty-eight infected children was the lowest of all the oxyuricides we have tested to date.

4. However, because of the ancient reputation of garlic as a "popular remedy" for pinworm infection substantiated in part by medical research, and because of the possibility of some error in our garlic study, we are of the opinion that garlic should be tried again both by us and other groups after some of the details of dehydrated garlic powder dosage have been confirmed. The complete lack of toxicity and the low cost of dehydrated garlic powder would make it, in our opinion, an ideal oxyuricide if repeated studies could confirm the high cure rates obtained by other researchers.

5. Terramycin in a reduced dose of 5 mg. per pound of body weight cured only 38 per cent of fifty-nine infected children. This dose, one-half of the dose we reported on in an earlier study, apparently is not enough to produce an effective cure rate.

The authors express their appreciation to Dr. Samuel Militello, the medical director of the German Roman Catholic Orphanage, for his permission to conduct this study at the German Roman Catholic Orphanage.

*Piperazine hexahydrate as syrup of Antepar Citrate was supplied by the Burroughs-Wellcome Company.

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RADIOCARDIOGRAPHY IN CONGENITAL HEART DISEASE

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THE purpose of this study was to explore the technique of radiocardiography as a possible diagnostic aid in children with congenital heart disease. This method was first described and used by Prinzmetal and associates,[1, 2] and subsequently by Waser and Hunzinger[3] and Shipley and coworkers.[4] These studies were concerned with the use of this technique in adults with normal hearts and those in congestive failure, although Prinzmetal included one radiocardiogram on an adult with a patent ductus arteriosus. More recently, Luisada and collaborators[5] described technical modifications of radiocardiography.

During the past fifteen months this method was used in over 100 children with congenital cardiac defects and twenty-two children with normal hearts. This study is still in progress and not complete, so that this report is preliminary in nature. The children with congenital heart disease selected were those in whom the diagnosis was verified by angiocardiography or catheterization. Most of the children were operated upon, and the diagnosis was then established, and in those who died the definite anatomical diagnosis was available at post-mortem examination.

METHOD

The instrument used in this investigation was a scintillation counter fitted with a sodium iodide, thallium activated crystal as shown in Fig. 1. The crystal is a cylinder one inch in diameter and one inch thick. The efficiency of this counter for the detection of gamma rays emitted by I^{131} is approximately 50 per cent. The output of the scintillation counter is fed into a counting rate meter connected to an Esterline-Angus graphic recorder. The response of the counting rate meter to the signal supplied by the scintillation counter is exponential with respect to time. For the measurements described in this paper, the time constant of the instrument was set to such a value as to give a half period of approximately one second.

A single counter was employed and placed over the midsternal line at the fourth interspace. Sterile diiodofluorescein tagged with I^{131} was used. Ten microcuries of diiodofluorescein, representing a volume of approximately 0.05 c.c., were carefully measured in a tuberculin syringe, and a venipuncture was performed in the antecubital fossa. One-half cubic centimeter of blood was withdrawn into the syringe containing the dye. The entire extremity was elevated above heart level, and at a given signal the injection was made as rapidly as possible with the recording device running at a constant speed. No sedation was used in order to simplify the procedure.

From the Departments of Pediatrics and Radiology, Washington University School of Medicine, and the St. Louis Children's Hospital.

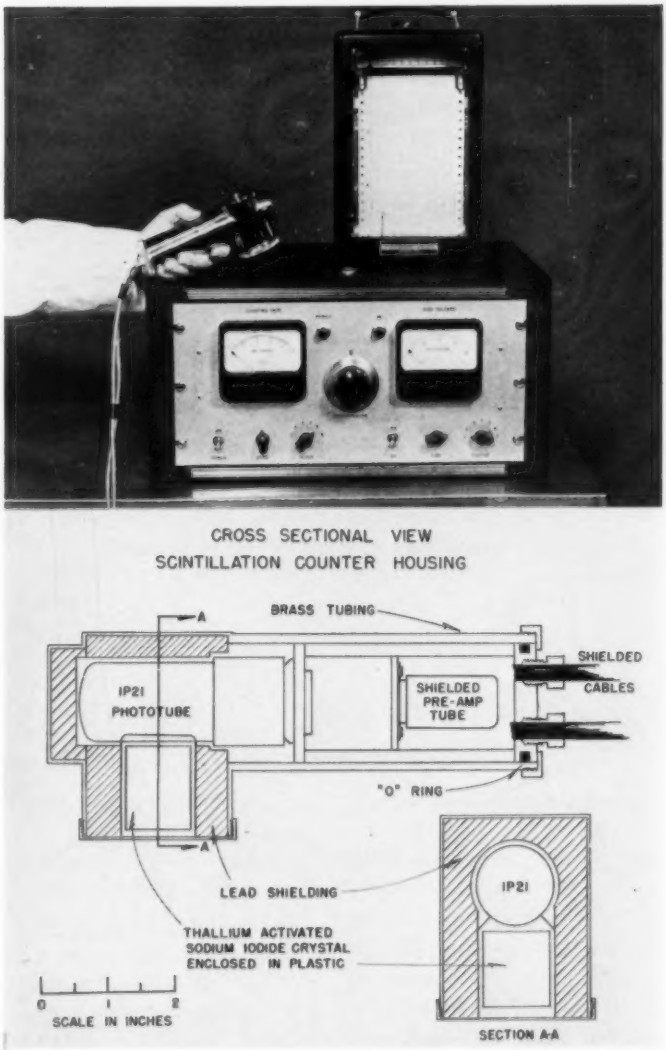

Fig. 1.—The scintillation counter and Esterline-Angus recording device used for radiocardiography.

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OBSERVATIONS ON CHILDREN WITH NORMAL HEARTS

A control group of twenty children between the ages of 2 and 10 years, who did not have any evidence of heart disease, was first studied. The type of curve obtained is shown in Fig. 2, and this showed a prompt rapid initial upswing which occurred within 3 seconds after injection of the radioactive material, followed by a less rapid downswing to form the first peak of the curve. The duration of this curve was 12 to 13 seconds when measured from the beginning of the upward deflection to the lowest point reached by the descending limb. This was usually followed by a low, flat-peaked secondary rise beginning 16 to 17 seconds after injection and lasting 10 seconds or less. A final base line was reached which was 40 to 50 per cent of the maximum amplitude of the first peak. Exact time measurements were not attempted, but this will be done at a future time when more data are accumulated and the significance of the curves is better understood.

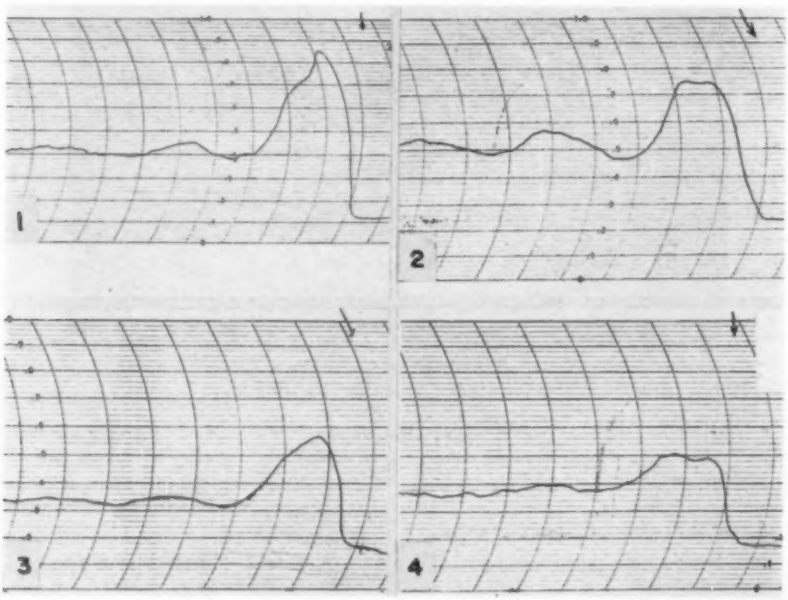

Fig. 2.—Radiocardiograms in normal children. The time interval between vertical lines is 4 seconds.

OBSERVATIONS ON CHILDREN WITH CONGENITAL CARDIAC ABNORMALITIES

Four children with uncomplicated patent ductus arteriosus were studied before and after surgical ligation. Preoperatively, the radiocardiogram in all four children showed a prompt rise after injection, followed by a downswing which tended to be prolonged. No second peak was observed. Following surgical ligation, an appreciable change in contour was noted. The descending limb of the

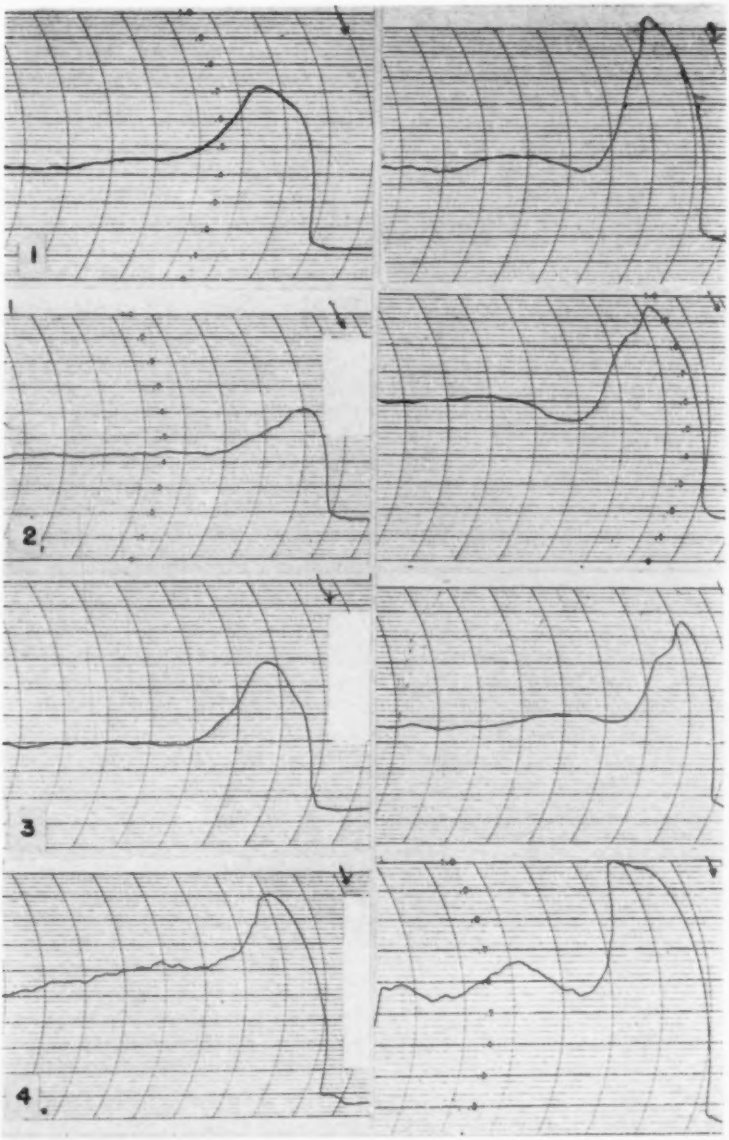

Fig. 3.—Radiocardiograms in patent ductus arteriosus before and after surgical ligation. At the left appear the preoperative tracings obtained. To the right is the postoperative tracing in each child: *1*, S. C.; *2*, M. H.; *3*, D. H.; *4*, D. W.

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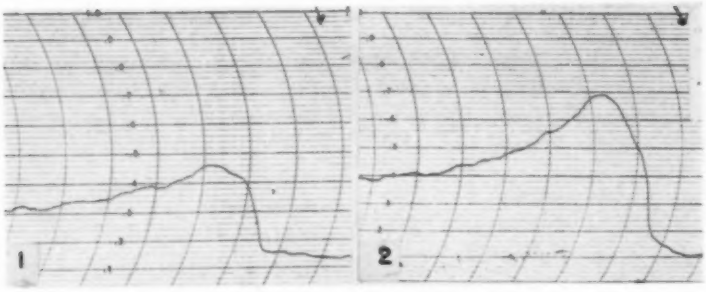

Fig. 4.—Radiocardiograms in Eisenmenger complex: *1*, T. Z.; *2*, J. S.

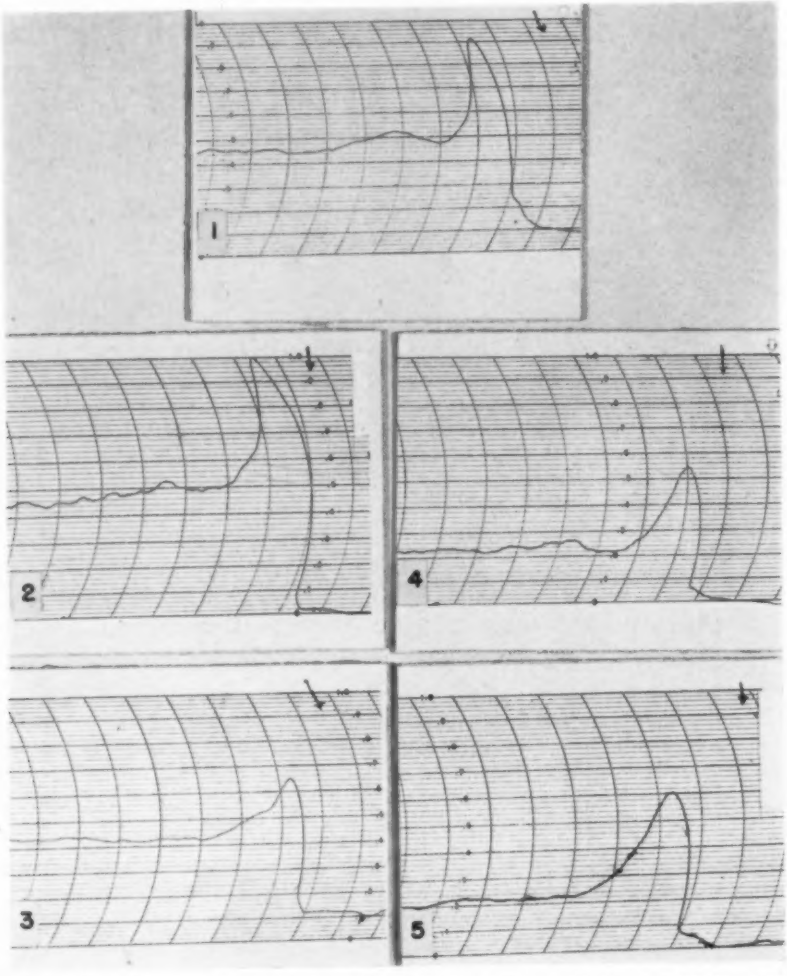

Fig. 5.—Radiocardiograms in tetralogy of Fallot: *1*, P. T.; *2*, L. L.; *3*, J. L.; *4*, W. B.; *5*, L. H.

first peak fell more abruptly and in turn was followed by a low-peaked secondary rise similar to that observed in normal children. The tracings of these four patients are shown in Fig. 3.

Two patients (T. Z. and J. S.) with Eisenmenger complex were examined in a similar manner, and the curves were much like those obtained in patients with a patent ductus and are shown in Fig. 4. At present we do not have an explanation for the striking similarity of the tracings in these two types of congenital malformations. It should be emphasized that the diagnosis of Eisenmenger complex was not verified at necropsy and was made after catheterization or angiocardiographic studies, the results of which will be found at the end of the paper in case summaries 1 and 2.

Five patients with tetralogy of Fallot had radiocardiograms before operation. Examination of the curves as shown in Fig. 5 reveals a prompt, almost vertical rise after injection of the dye. A narrow peak is formed as the descending limb falls abruptly, and in three of the five curves a secondary rise is seen which occurs 2 to 3 seconds earlier than in the normal curves. The marked difference in contour between the tracings of Eisenmenger complex and tetralogy of Fallot is most striking.

The diagnosis of tetralogy of Fallot was made by catheterization studies in all five patients, and the results are summarized in Table I. All patients except one had a definite pressure gradient between the right ventricle and the pulmonary artery. In patient L. H. the pulmonary artery could not be catheterized. In four patients the diagnosis was verified at operation and in one at necropsy.

In one of the patients (L. H.) simultaneous curves were obtained over the right nipple and over the midsternal line at the fourth interspace before and after operation as shown in Fig. 6. The tracing obtained over the midsternal line at the fourth interspace did not change appreciably after operation; however, the almost flat curve obtained over the right nipple preoperatively underwent a significant change following the creation of a shunt and may possibly represent increased pulmonary blood flow. It is felt that the tracing obtained when the counter was over the nipple might represent chiefly the concentration of radioactive material in the pulmonary circuit, for on the adult chest the counter can be moved a relatively greater distance from the heart than in the infant and young child.

One patient (M. B.) who was found to have a markedly enlarged heart when subjected to cardiac catheteriza-

TABLE I. SUMMARY OF CLINICAL FINDINGS IN FIVE PATIENTS WITH TETRALOGY OF FALLOT

PATIENT	AGE (YR.)	SEX	Hb. GM. %	ECG	RV PRESS. MM. HG	PA PRESS. MM. HG	SURGICAL PROCEDURE
P. T.	5	F	20.0	RV hypertrophy	90/5	15/5	Blalock
L. L.	4½	F	17.0	RV hypertrophy	85/6	15/7	Pulmonary valvulotomy
J. L.	4	M	15.5	RV hypertrophy	80/5	20/5	Pulmonary valvulotomy
W. B.	4	F	21.4	RV hypertrophy	70/5	5 (mean)	Autopsy
L. H.	17	F	20.6	RV hypertrophy	100/0	—	Blalock

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tion and angiocardiography was subsequently explored. The findings are related in case summary 3. It was felt that the most likely diagnosis was Ebstein's deformity. This patient was also studied by radiocardiography, and the tracing, as shown in Fig. 7, showed an abrupt rise and a very slow decline over a period of 26 seconds which seemed to coincide with the persistence of Urokon in the right heart as demonstrated by the angiocardiographic study.

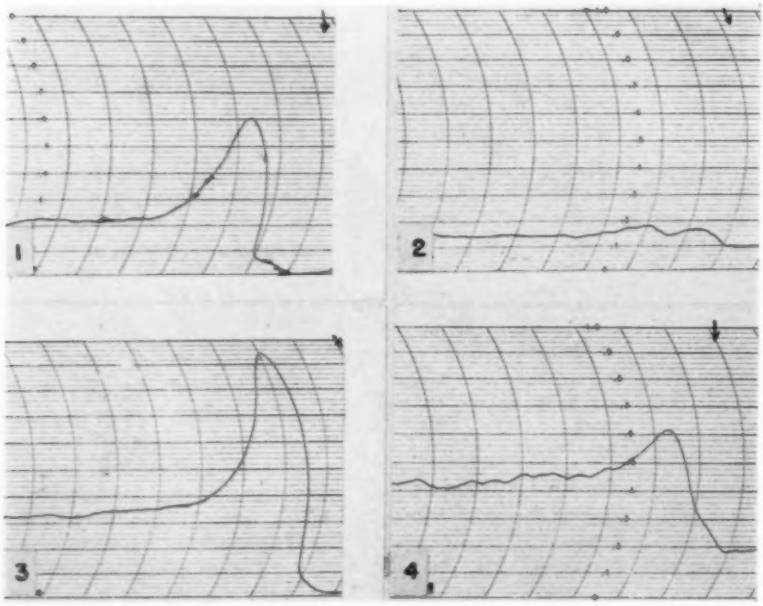

Fig. 6.—*1*, Tracing obtained over midsternal line at fourth interspace preoperatively in patient L. H. with tetralogy of Fallot. *2*, Preoperative tracing taken over right nipple. *3*, Postoperative tracing obtained over midsternal line at the fourth interspace. *4*, Postoperative tracing obtained over the right nipple.

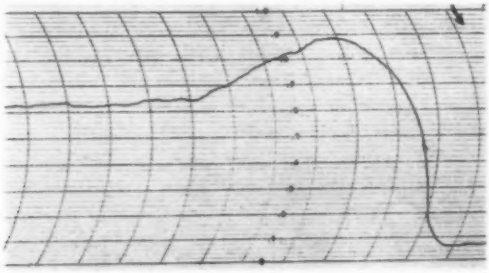

Fig. 7.—Radiocardiogram in M. B. (questionable Ebstein's disease).

In an infant with tricuspid stenosis, a patent foramen ovale, and fibroelastosis of the left ventricle verified

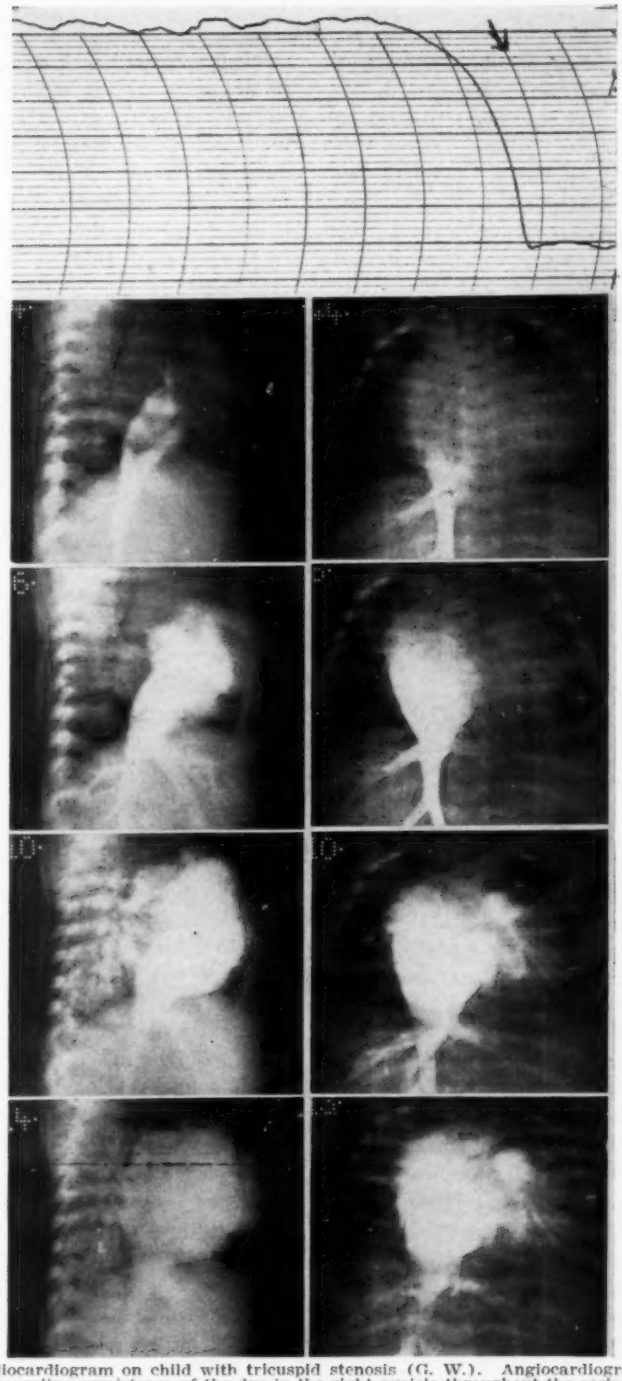

Fig. 8.—Radiocardiogram on child with tricuspid stenosis (G. W.). Angiocardiogram is shown revealing persistence of the dye in the right auricle throughout the series.

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at necropsy, a similar radiocardiogram was obtained, as shown in Fig. 8. The tracing revealed a prompt rise which persisted without decline for a period of 40 seconds. Upon examination of the angiocardiogram in Fig. 8, one sees the persistence of the Urokon in the right heart, and this suggests an explanation for the plateaulike curve of the radiocardiogram.

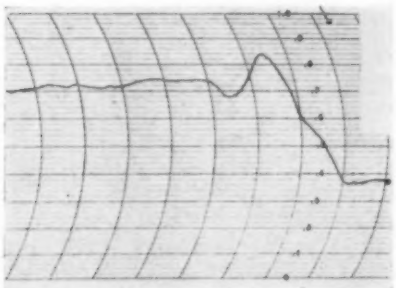

Fig. 9.—Radiocardiogram on a child (S. C.) with transposition of the great vessels.

A single observation was obtained on a 4-year-old child (S. C.) with complete transposition of the aorta, levoposition of the pulmonary artery, and an interventricular septal defect[6] verified at necropsy. The radiocardiogram, as shown in Fig. 9, revealed an upswing which was prompt and a small peak which was formed by a short descending limb. This was followed by a second rise which persisted on a high base line. The pattern of cardiac blood flow is quite complicated in transposition of the great vessels, and since this is a single study, it would be premature to attempt to explain the significance of this radiocardiogram.

One patient who had complete transposition of the great vessels with pulmonary stenosis verified at necropsy was also studied with this method. The tracing, as shown in Fig. 10, is similar to the radiocardiograms of the tetralogy group and, of course, different from the curve obtained in Case S. C. described above. This patient, S. S., was included originally in the tetralogy of Fallot group, and this is explained in the detailed case summary 4. In retrospect, we must conclude that this type of lesion would be extremely dif-

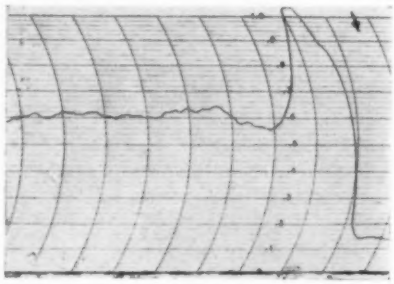

Fig. 10.—Radiocardiogram on S. S.

ficult to diagnose by any technique. This child had the benefit of all available and accepted diagnostic techniques and was subjected to surgical exploration, yet the correct anatomical diagnosis was not made until necropsy. A post-mortem review of the angiocardiogram and catheterization results did not demonstrate where this case differed from that of tetralogy of Fallot.

A child, M. S., whose course and studies in the hospital, as reviewed in case summary 5, pointed to a diagnosis of tricuspid atresia, nonfunctioning right ventricle, and pulmonary stenosis, was examined preoperatively and postoperatively by this method. The radiocardiogram before operation, as shown in Fig. 11, showed a prompt rise, followed by a slow decline to a high base line. Postoperatively, the peak was less pronounced,

and the base line remained high. Here also the interpretation of the radiocardiogram will have to be delayed until more such cases are studied.

DISCUSSION

The method of radiocardiography is simple and safe. Diiodofluorescein was preferred as the test substance because of the easy availability, rapid excretion, and 8-day half-life of I^{131} in contrast to radioactive sodium, which has a short half-life of 14.8 hours or iodinated radioactive human serum albumin, which is not excreted as rapidly.

The true significance of the radiocardiogram is still imperfectly understood. Although other investigators[1, 2, 3, 4] have stated that the two upward deflections of the radiocardiogram represent first right, then left heart concentration of the radioactive substance, we believe that it may be chiefly the activity in the right heart that is reflected in the tracing. An attempt to verify this was carried out by doing a simultaneous radiocardiogram and angiocardiogram on a 5-month-old child with hydrocephalus but no evidence of cardiac disease. Simultaneous anteroposterior and lateral roentgenograms were taken at one-second intervals for a total of ten exposures. The first exposure coincided with the apex of the first upward deflection of the radiocardiogram as shown in Fig. 12. The films taken a few seconds after the beginning of the descending limb of the radiocardiographic curve showed opaque material in the right heart and pulmonary artery. The left ventricle and aorta were not opacified until well after the initial wave had reached a plateau. No secondary rise was noted in the radiocardiogram that could be correlated with filling of the left ventricle. This experiment suggests that the radiocardiogram reflects primarily the concentration of the radioactive tracer substance in the right heart, but more evidence is obviously necessary to establish this conclusively.

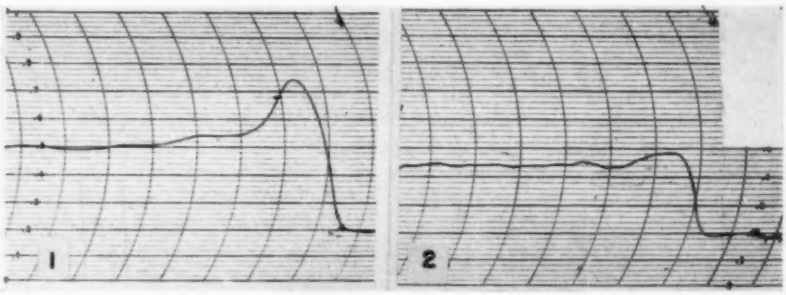

Fig. 11.—Radiocardiogram on an infant (M. S.) with tricuspid atresia, nonfunctioning right ventricle, and pulmonary stenosis. *1*, Preoperative; *2*, postoperative.

The tracings obtained with the method used in this study are grossly similar to the dye dilution curves in cyanotic congenital heart disease recently reported by Swan and associates[7] who employed Evans blue and followed the dilution of this dye in the blood stream with an earpiece oximeter. In Swan's method, the dye was usually injected during cardiac

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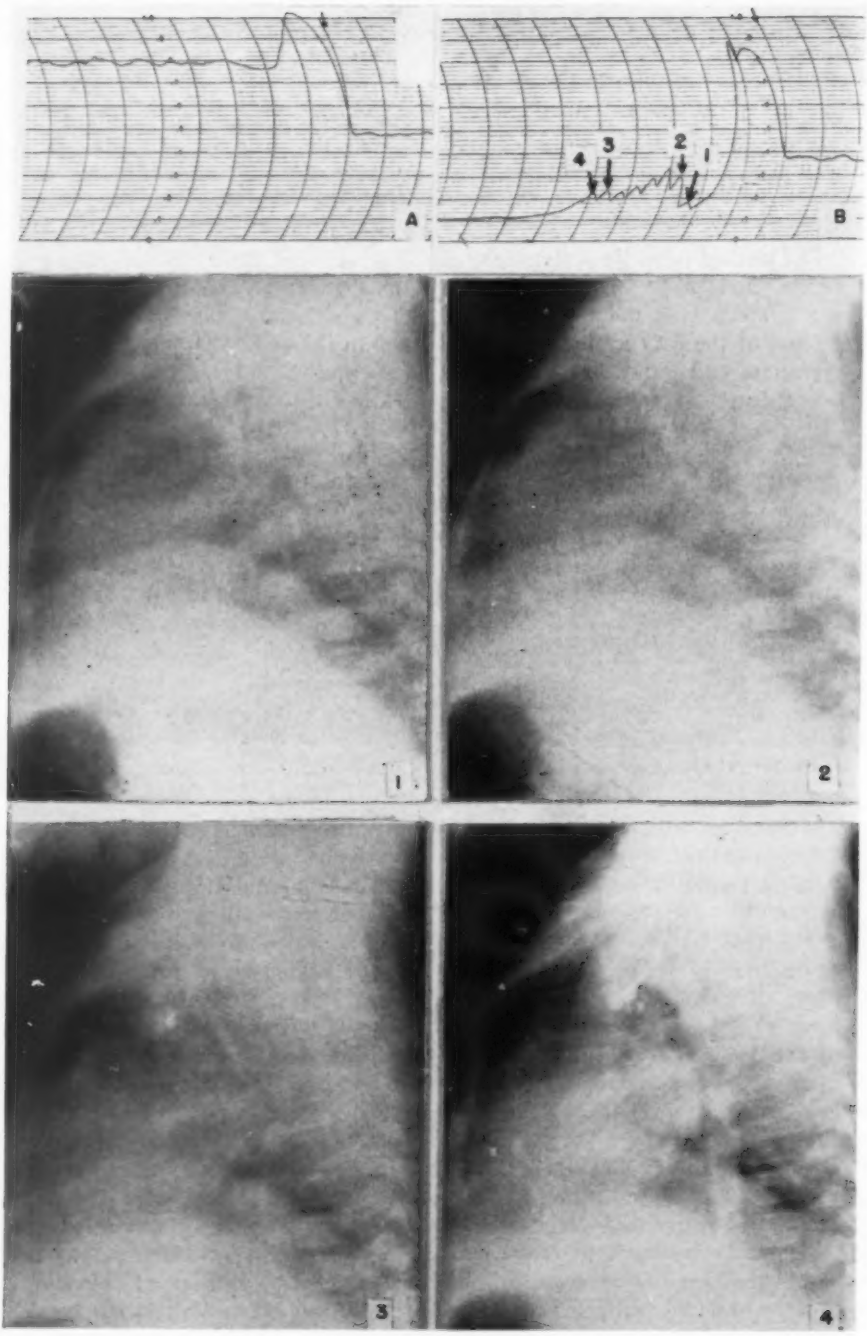

Fig. 12.—*A*, Radiocardiogram on hydrocephalic infant with a normal heart. *B*, Repeat radiocardiogram-angiocardiogram where top of peak was detected with scintillation counter. Each deflection of curve thereafter denotes firing of the x-ray tube. Numbers in *B* correspond to angiocardiograms below.

catheterization when the tip of the catheter was within the superior vena cava or within the right cardiac chambers. He believes that distinctive dye dilution curves can be obtained in different congenital cardiac malformations. Although he applied quantitative measurements to the curves obtained, a quantitative appraisal of the curves obtained with radiocardiography would be premature until more work has been done to establish the significance of the tracings.

The preoperative radiocardiograms of patients with patent ductus arteriosus seem grossly similar, but it is doubtful whether the curves will prove to be specific for the many other different types of cardiac anomalies. Cases of congenital heart disease which tend to produce dilatation or hypertrophy of the right auricle, right ventricle, or both, may prove to show similar tracings. This is suggested when one compares the curves in G. W. (Fig. 8), tricuspid stenosis with patent foramen ovale, and the probable case of Ebstein's disease (M. B., Fig. 7). In one patient (not included in this report), who was shown to have right ventricular hypertrophy and pulmonary arteriosclerosis at autopsy, the radiocardiogram was somewhat similar to the above curves. No cases of pure pulmonary stenosis or pulmonary stenosis associated with an interauricular septal defect were studied with radiocardiography, but it is probable that similar curves might be obtained.

The striking difference in the radiocardiographic tracings obtained in Eisenmenger complex and tetralogy of Fallot suggests that this method may prove valuable in their differential diagnosis without resorting to catheterization or angiocardiography. The narrow peak in patients with tetralogy of Fallot is not surprising since a portion of the venous blood is shunted directly to the systemic circulation through the overriding aorta. One would expect a similar curve in the Eisenmenger complex, for in this condition there is also a direct pathway for venous blood to be shunted through an overriding aorta. Ziegler[8] has shown in his studies that the circulation time from the right ventricle to the lip is reduced in both conditions. The radiocardiograms are, nevertheless, definitely different although we have no adequate explanation for this difference. We are aware that the number of patients studied is small, and reproducibility of the curves may not prove consistent as more cases are studied. Also, it should be remembered that our diagnosis of Eisenmenger complex was based upon angiocardiographic or catheterization findings that seemed to support the diagnosis, but autopsy confirmation of the anatomical diagnosis was not available.

If further studies indicate differences in the radiocardiograms in the Eisenmenger and tetralogy group, this method would be extremely useful as a diagnostic aid especially in infancy when one is confronted with the problem of the differential diagnosis of a slightly cyanotic infant and operation is not urgent. Radiocardiography, because of its simplicity and safety, may prove to be a valuable initial diagnostic aid in such a situation since one hesitates to resort to angiocardiography or catheterization because of the inherent risks involved. More studies are needed in normal children and those with congenital heart dis-

case to determine the influence of such factors as tachycardia, congestive failure, and respiration on the character of the radiocardiograms.

Although this is a preliminary report, these initial results are encouraging and point to this method as an aid in the diagnosis of congenital heart disease.

SUMMARY

1. The technique of radiocardiography has been employed to study twenty-two children with normal hearts and 100 children with congenital heart disease.

2. Different types of radiocardiograms were obtained in patients with patent ductus arteriosus, tetralogy of Fallot, Eisenmenger complex, and tricuspid atresia.

3. This method may be useful in differentiating patients with Eisenmenger complex from those with tetralogy of Fallot.

4. Although the exact physiological phenomena responsible for the types of curves obtained are not known, preliminary evidence suggests that the radiocardiogram is predominantly a reflection of the blood flow in the right heart.

CASE SUMMARIES

Eisenmenger Complex

CASE 1.—T. Z. was a 14-year-old white male with a history of sudden onset of cyanosis, dyspnea, and listlessness six months prior to admission. He appeared well developed and well nourished and was slightly cyanotic at rest. There was cardiac enlargement and a systolic murmur along the left sternal border. The hemoglobin was 16.4 grams per cent. Electrocardiograms showed evidence of right ventricular hypertrophy. Cardiac catheterization revealed right ventricular and pulmonary artery hypertension, and evidence of an interventricular septal defect. The most likely diagnosis was thought to be Eisenmenger complex.

CASE 2.—J. S. was an 11-year-old white male with a history of cyanosis since the age of 3 weeks. His early growth and development was normal, but subsequently seemed retarded. He suffered from exertional dyspnea and bouts of palpitation accompanied by cyanosis. Examination disclosed a fairly well-developed and well-nourished child with generalized cyanosis and marked clubbing of the fingers and toes. He was moderately dyspneic. The apical impulse was diffuse, and there was a loud precordial systolic murmur without a thrill. The hemoglobin was 16.2 grams per cent. An electrocardiogram showed sinus arrhythmia and right ventricular hypertrophy. Roentgenograms of the chest showed right ventricular enlargement and engorged pulmonary vessels. Cardiac catheterization was unsuccessful. Angiocardiography using 70 per cent Urokon was done and interpreted as showing a ventricular septal defect with overriding of the aorta. All of the findings seemed most compatible with a diagnosis of Eisenmenger complex.

Possible Ebstein's Deformity

CASE 3.—M. B. was a 15-year-old white female with a history of normal birth, growth, and development. When she was 6 years old, a heart murmur was first noted, and cardiac enlargement was present on x-ray. She attended school and was not limited in physical activities. Two months prior to hospitalization in St. Louis Children's Hospital in 1951 she described an episode of dyspnea and pedal edema which lasted about a week and disappeared without treatment. At this time she appeared well developed and well nourished and in no distress. There was no cyanosis or clubbing. The heart was enlarged to the left anterior axillary line, and the P.M.I. was diffuse. A systolic thrill was palpable over the precordium. There was a left

basilar systolic murmur and an apical diastolic murmur. Her blood pressure was 110/70; the hemoglobin was 14.9 grams per cent. An electrocardiogram showed right ventricular hypertrophy. Roentgenograms of the chest revealed marked right ventricular enlargement and pulmonary vascular shadows of decreased caliber, suggesting pulmonic stenosis. An angiocardiogram revealed a markedly enlarged right auricle in which the contrast medium persisted, and a rather small right ventricle. Cardiac catheterization revealed normal pressures in the right ventricle and pulmonary artery with normal oxygen saturations. It was felt, however, that pulmonary stenosis was still a possibility, and a thoracotomy was performed but revealed only marked enlargement of the right heart without evidence of pulmonary stenosis. It was thought that the findings might be compatible with Ebstein's disease.

Complete Transposition of the Great Vessels With Pulmonary Stenosis

CASE 4.—S. S., a 2½-year-old white male, was first seen at the St. Louis Children's Hospital at age 5½ months with a history of cyanosis since birth and intermittent bouts of mild dyspnea. Physical examination at the time revealed an intensely cyanotic infant with definite clubbing of the fingers and toes. A systolic murmur was audible over the entire precordium. Hemoglobin was 22 grams per cent. Electrocardiogram: Right ventricular hypertrophy. Chest x-ray: No cardiomegaly; the pulmonary vessels appeared of small caliber, and there was a concavity in the region of the left pulmonary artery segment. A diagnosis of tetralogy of Fallot was made, and the child was followed periodically. At the age of 2½ years he began to have facial and pedal edema and mild bouts of dyspnea. In May, 1953, he was admitted for study. Physical examination and the electrocardiographic and x-ray findings were unchanged. Cardiac catheterization revealed right ventricular hypertension (62/12 mm. Hg), a probable interventricular septal defect, and dextroposition of the aorta. It was not possible to enter the pulmonary artery. He was also studied by angiocardiography, and this revealed an extremely dextroposed aorta, simultaneous filling of the aorta and pulmonary artery, but a relatively small amount of dye was visualized in the pulmonary vessels. It was felt that these findings were also compatible with a diagnosis of tetralogy of Fallot. A Potts-Smith anastomosis was performed, and at the time of operation the pulmonary vessels were observed to be small. Postoperatively, there was marked relief of cyanosis and dyspnea.

He got along quite well until three days before his final admission, Aug. 23, 1953, when he developed fever and vomiting. Twelve hours after admission he suddenly expired. Autopsy revealed complete transposition of the great vessels, pulmonary valvular stenosis, a high interventricular septal defect, and an aberrant vessel arising from the aorta and communicating with the right branch of the pulmonary artery.

Nonfunctioning Right Ventricle With Pulmonary Stenosis

CASE 5.—M. S. was an 11-month-old white male with a history of cyanosis noted soon after birth and an onset of generalized convulsive seizures at age 6 months. Physical examination revealed a frail, fussy, cyanotic infant who was unable to sit without support. Systolic blood pressure was 100-119 mm. Hg (flush technique).[9] There was definite clubbing of the fingers and toes. The heart was enlarged to the left, and a rough systolic murmur was heard over the entire precordium. The liver was not enlarged, and there was no peripheral edema. The hemoglobin was 13.9 grams per cent. An electrocardiogram revealed sinus tachycardia, questionable auricular hypertrophy, and evidence of myocardial disease. Chest roentgenograms showed small pulmonary vessels, suggesting pulmonic stenosis. The heart was enlarged but showed a flattening of the lower right border in the frontal and right anterior oblique projection, sug-

gesting hypoplasia of the right ventricle. An angiocardiogram with 70 per cent Urokon showed sequential filling of the right and left auricles and left ventricle and aorta. The right ventricle was never visualized. A diagnosis of tricuspid atresia with an interauricular septal defect, nonfunctioning right ventricle, and pulmonary stenosis was made. A Blalock procedure was carried out with marked improvement of cyanosis and dyspnea.

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TREATMENT OF DIARRHEA WITH COMBINED AUREOMYCIN AND TRIPLE SULFONAMIDES (AUREOMAGMA)

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ADVANCES in fluid and electrolyte therapy during the past fifteen years are largely responsible for the reduction in mortality associated with diarrhea during infancy. However, chemotherapeutic and antibiotic agents are also important in the management of these cases for the following reasons: (1) treatment of primary intestinal infection, (2) therapy of parenteral infections associated with diarrhea, and (3) prophylactically, to prevent intercurrent infection, to which the debilitated child with diarrhea is more susceptible.

It has been demonstrated that combinations of various drugs decrease the emergence of resistant strains of bacteria when compared with the use of these drugs singly.[1, 2, 3, 4] For this reason many combinations such as penicillin and streptomycin, penicillin and sulfonamides, as well as combinations of the newer antibiotics, have been advocated. The present study concerns the use of a combination of Aureomycin and triple sulfonamides in a liquid preparation, known as Aureomagma, in the management of diarrhea in infants and children. The therapeutic efficacy of this combination is compared with the use of several agents, singly or in combination, frequently used in the management of diarrhea.

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Aureomagma is a suspension of Aureomycin and triple sulfonamides in a tart-flavored vehicle. Four cubic centimeters contain the following:

Aureomycin calcium	125 mg.
Sulfadiazine	167 mg.
Sulfamerazine	167 mg.
Sulfamethazine	167 mg.
Methyl Paraben	0.08%
Propyl Paraben	0.02%
Flavored vehicle, q.s.	4 c.c.

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CLINICAL MATERIAL AND THERAPY

Selection of Patients.—The patients were treated in The John Gaston Children's Hospital and were divided into two groups: (1) "comparison" group, fifty patients, and (2) Aureomagma treated, fifty patients. These shall, hereafter, be referred to as Group I and Group II, respectively. From Tables I, II, and III it may be observed that the age, type of infection, and severity of the diarrhea were comparable in the two groups. The period of observations for the patients in Group II and for forty patients in Group I extended from Sept. 14 to Nov. 14, 1952. Ten additional patients originally included in Group I were infected with one of the Salmonella group of organisms (paratyphoid B), and were eliminated from consideration because they would have influenced the results unjustifiably in favor of the Aureomagma treatment. Therefore, observations were made on ten patients in Group I during the period from June 12 to Sept. 14, 1952.

Drug Therapy.—Drug therapy in the two groups was as follows:

Group I. Antibiotics and chemotherapeutic agents, singly or in combination, as listed in Table II, were used among this group of patients. It is to be emphasized that in no instance was Aureomycin used in combination with sulfonamides in this group of patients.

Group II. The dosage of Aureomagma was calculated to supply 12.5 mg. of Aureomycin and 50 mg. of triple sulfonamides per kilogram per twenty-four hours, based on the admission weight. The original preparation was diluted 1:10 and administered at six-hour intervals. The mixture was begun in most cases within six hours after admission, allowing time for institution of parenteral fluid therapy. It is of interest that vomiting was noted in only one instance following the administration of Aureomagma, although some of the patients had vomited prior to admission.

Parenteral Fluid Therapy.—Parenteral fluid therapy was similar in the two groups. This included the intravenous and subcutaneous administration of M/6 sodium lactate, subcutaneous infusion of Ringer's solution with added potassium chloride (1.2 meq. per kilogram per twenty-four hours), intravenous infusion of 5 per cent glucose in distilled water, and whole blood transfusion. Total fluid intake during the first twenty-four hours ranged between 175 and 215 c.c. per kilogram.

Milk and solid foods were withheld during this period, after which they were usually well tolerated.

TABLE I. CLINICAL CLASSIFICATION OF PATIENTS

AGE	MILD		MODERATE		SEVERE	
	GROUP I	GROUP II	GROUP I	GROUP II	GROUP I	GROUP II
1 mo.	0	0	0	2	2	5
1-3 mo.	1	3	8	8	8	10
4-6 mo.	0	0	8	4	3	5
7-12 mo.	0	1	4	2	4	2
1-15 yr.	3	0	6	8	3	0
Total	4	4	26	24	20	22

Data Collected.—The following data were collected and tabulated on all patients at the time of admission and during hospitalization:

1. Age, race, and sex.
2. Days ill prior to admission.
3. Number and character of stools, and time of appearance of the first formed stool.
4. Degree of dehydration.
5. Daily weight.
6. Degree of lethargy.
7. Duration of hospitalization.
8. Duration and extent of parenteral fluid therapy.
9. Clinical response, as judged by the attending and house staffs.
10. Laboratory studies included:
    (a) Plasma bicarbonate.
    (b) Serum chlorides.
    (c) Hemograms.
    (d) Urinalysis.
    (e) Blood cultures.
    (f) Stool cultures.
    (g) Other tests, such as serum agglutinations, plasma and erythrocyte sodium, potassium and chloride levels, were occasionally performed.

Classification by Degree of Severity of Diarrhea.—On the basis of the above information, it may be observed in Table I that the patients were evenly

distributed in the two groups, and were classified as mild, moderate, or severe.

The *mildly ill* patients passed five to ten stools on the day of admission and exhibited only slight dehydration. The temperature ranged from normal to 100° F., and the acidosis was mild, with a plasma bicarbonate greater than 20 meq. per liter. These patients were in no immediate danger.

The *moderately ill* patients passed ten to fifteen stools during the twenty-four hours prior to admission, and presented moderate but obvious dehydration, with loss of tissue turgor. The temperature ranged from 101 to 103° F., and the acidosis was moderately severe, with the plasma bicarbonate between 10 and 20 meq. per liter. It appeared that these patients would soon be in danger if allowed to go untreated.

The *severely ill* patients passed fifteen to twenty, or more, stools during the twenty-four hours prior to admission, and vomiting was a frequent symptom. They were obviously dehydrated, with marked loss of tissue turgor, and usually had a temperature above 103° F. They were lethargic, exhibited Kussmaul breathing (unless in extremis), and the acidosis was severe, with the plasma bicarbonate less than 10 meq. per liter. These patients constituted medical emergencies.

METHOD OF EVALUATION

In an effort to determine the comparative value of Aureomagma and the other therapeutic agents used in this study, the data were evaluated according to the following categories:

1. Incidence and duration of positive stool cultures.
2. Incidence and duration of positive blood cultures.
3. Duration of fever.
4. Duration and severity of diarrhea.
5. Extent and duration of parenteral fluid therapy.
6. Length of hospitalization.
7. Untoward effects of Aureomagma.
8. Blood sulfonamide levels.

Stool cultures were carried out in 95 per cent of the cases of both groups, and included at least two, and usually three, cultures obtained by rectal swab during the early period of hospitalization. The patients with positive stool cultures are described in Tables II and III. Stool cultures were positive for *Shigella paradysenteriae* in 20 per cent (ten patients) of the cases in each group; viral cultures and typing for the pathogenic strains of the colon group of organisms were not carried out. In those cases with stool cultures positive for *Sh. paradysenteriae,* it is clear that Aureomagma exerted a beneficial influence, the stools uniformly becoming negative after the first or second day of treatment (Table III). Stool cultures from five patients in Group I were positive on the second or third day, and may have remained positive beyond that time since cultures were usually discontinued after the third hospital day. Patient 9 had positive stools on the first, third, and fifth hospital days (Table II). As determined by a follow-up of hospital and clinic readmissions, one patient from each group with positive stool cultures at the time of this study was readmitted to the hospital. Patient 5 in Group I (Table II), and Patient 6 in Group II (Table III), were readmitted sixty-five and fourteen days, respectively, after discharge. The readmission diagnosis in each of these cases was "bronchopneumonia and

diarrhea." However, repeated stool cultures were negative, and the patients responded promptly to penicillin-streptomycin and Aureomagma therapy, respectively.

tive *Staphylococcus aureus* in a severely ill patient. Blood culture from one of the severely ill patients in Group I was positive for *Staph. aureus* (not coagulase tested) and a gram-negative

TABLE II. DESCRIPTION OF PATIENTS IN GROUP I WITH POSITIVE STOOL CULTURES

PATIENT NO.	AGE	CLASSIFICATION	RESULTS OF STOOL CULTURES — HOSPITAL DAY 1	2	3	4	5	ORGANISM	THERAPY
1.	6 mo.	Mild	+	–	–			*Sh. paradysenteriae* Hiss-Park	Terramycin
2.	2 yr.	Moderate	+	–	–			*Sh. paradysenteriae*	Penicillin-Terramycin
4.	2 yr.	Mild	+		–		–	*Sh. paradysenteriae* Hiss-Park	Penicillin-sulfadiazine
5.	1 yr.	Moderate	+	–	–	–		*Sh. paradysenteriae* Hiss-Park	Penicillin-aureomycin
6.	8 mo.	Severe	–	–	+			*Sh. paradysenteriae*, *Salmonella* Schottmülleri	Streptomycin-penicillin-Terramycin
7.	4 mo.	Severe	+	+	+			*Sh. paradysenteriae* Hiss-Park	Streptomycin-penicillin-Terramycin
8.	5 wk.	Severe	+	+	+			*Sh. paradysenteriae* Hiss-Park	Penicillin
9.	15 mo.	Severe	+		+		+	*Sh. paradysenteriae* Hiss-Park	Penicillin-streptomycin
10.	3 yr.	Moderate	–	+	+			*Sh. paradysenteriae* Hiss-Park	Penicillin-streptomycin
27.	3 mo.	Moderate	+	–		–		*Sh. paradysenteriae* Hiss-Park	Penicillin-Terramycin

TABLE III. DESCRIPTION OF PATIENTS IN GROUP II WITH POSITIVE STOOL CULTURES

PATIENT NO.	AGE	CLASSIFICATION	RESULTS OF STOOL CULTURE — HOSPITAL DAY 1	2	3	4	5	ORGANISM
1.	9 mo.	Mild		+	–	–		*Sh. paradysenteriae*
3.	2 yr.	Moderate	+	+	–			*Sh. paradysenteriae* Hiss-Park
6.	3 mo.	Severe	+	–	–			*Sh. paradysenteriae* Hiss-Park
8.	6 mo.	Severe	+	–				*Sh. paradysenteriae* Hiss-Park
			(also negative, days 7, 8, 9)					
11.	3 yr.	Moderate	+	–	–			*Sh. paradysenteriae*
34.	4 yr.	Moderate	+		–	–		*Sh. paradysenteriae*
36.	4 mo.	Moderate	+	–	–			*Sh. paradysenteriae*
43.	5 yr.	Moderate	+	–	–			*Sh. paradysenteriae*
49.	4 mo.	Moderate	+	–				*Sh. paradysenteriae* Hiss-Park
50.	3 mo.	Severe		+		–		*Sh. paradysenteriae*

Blood cultures were obtained from nineteen patients in Group II and 13 in Group I. Two cultures of the former group were positive; one for *Escherichia coli* in a moderately ill patient, and another for coagulase-negative spore bearer. In each of the three cases these organisms could not be correlated with the clinical picture, and were thought to be contaminants.

Duration of fever was essentially the same in both groups, with 81 per

cent of Group II and 79 per cent of Group I becoming afebrile by the third day of hospitalization.

The *duration of diarrhea* was longer in Group I. Many in Group II improved as early as the third day of hospitalization (Table IV). Eighty-two per cent of the patients in Group II had formed stools on the fifth day of hospitalization, whereas seven days were required for the appearance of formed stools in a comparable number of patients among Group I. Inspection of the data reveals that the longer duration of the diarrhea in the patients in Group I was not attributable to the use of Terramycin in some of the cases.

The *duration of parenteral fluid therapy* (Table V) was longer in Group I than in Group II. The formulas were equally well retained in both groups. The only explanation which we can offer for this observation is that infection and diarrhea were controlled earlier in Group II. On the third and fourth hospital day, respectively, 11 and 4 per cent of the patients in Group II required fluid therapy, whereas 54 and 38 per cent of Group I required fluid therapy at this time.

The *average length of hospitalization* (Table VI) was definitely shorter for Group II and 44 per cent of Group I group, compared with 8 per cent for Group I, were discharged by the fifth day of hospitalization. On the tenth day of hospitalization, 14 per cent of Group II and 44 per cent of Group I were still confined to the hospital.

In order to determine any *untoward effects of Aureomagma*, the patients were observed specifically for: (a) accentuation of diarrhea, (b) vomiting, or increased vomiting, (c) skin eruptions, (d) alteration of hemogram, and (e) evidence of renal damage. No clinical or laboratory indication of the above was noted. The patients tolerated the oral medication very well, and vomiting was absent in 98 per cent of the cases.

One severely ill patient, aged 3 months, with negative stool cultures, and while receiving Aureomagma, developed osteomyelitis of the femur, with a femoral abscess at the site of a femoral venipuncture ten days after admission. This patient had recovered from his diarrhea. Cultures from the femoral abscess yielded a coagulase-positive hemolytic *Staph. aureus*. Recovery was complete following large doses of penicillin and streptomycin.

The *serum sulfonamide levels in six patients receiving Aureomagma* were

TABLE IV. DURATION OF DIARRHEA IN GROUPS I AND II

	PER CENT OF PATIENTS WITH FORMED STOOL						
	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	10TH DAY
Group I	8	16	40	56	75	86	96
Group II	8	36	58	82	92	96	100

TABLE V. DURATION OF PARENTERAL FLUID THERAPY

	PER CENT OF PATIENTS REQUIRING PARENTERAL FLUID THERAPY			
	1ST DAY	2ND DAY	3RD DAY	4TH DAY
Group I	98	71	54	38
Group II	96	31	11	4

TABLE VI. LENGTH OF HOSPITALIZATION

	PER CENT OF PATIENTS DISCHARGED		
	5TH DAY	10TH DAY	15TH DAY
Group I	8	56	82
Group II	36	86	96

determined, using sulfadiazine as a standard (Table VII). As stated above, the dosage of triple sulfonamide was 50 mg. per kilogram (½ grain per pound) per twenty-four hours. The sulfonamide levels in these patients (ten determinations) ranged from 2.3 to 10.4 mg. per cent. The levels of 4.6 mg. per cent, or greater, are of interest in view of the relatively low dosage of the sulfonamides. We could not correlate the blood concentrations with the degree of kidney maturity as determined by the age of the patients, or with the severity of the diarrhea.

Table VII. Blood Sulfa Levels in Six Patients Receiving Aureomagma

PATIENT NO.	SEX	AGE	CLASSIFICATION	HOSPITAL DAY	SULFA LEVEL MG./%
40	M	4 mo.	Severe	18	2.9
				20	3.3
41	M	2 mo.	Moderate	10	4.6
43	M	5 yr.	Moderate	8	5.9
				10	7.8
44	M	7 wk.	Severe	11	2.3
				13	2.5
45	F	5 mo.	Moderate	4	6.3
				6	5.0
47	M	9 mo.	Severe	3	10.4

COMMENTS

Aureomagma, which combines the chemotherapeutic effect of triple sulfonamides with the antibiotic effect of Aureomycin, appears to be a highly desirable compound in the management of diarrhea attributable to the *Sh. paradysenteriae* group of organisms, as well as in patients in whom no infectious agent could be isolated. Furthermore, it was effective in preventing secondary infections, except in one case which developed a femoral abscess and osteomyelitis following venipuncture. It is to be emphasized that the dosage of Aureomycin and sulfonamide, administered in the form of Aureomagma, is in the lower range generally recognized as therapeutically effective for these agents singly.[5, 6] Therefore, it appears that this combination might exert an additive effect.

Patients with positive stool cultures ("infected") were compared with those having negative stool cultures ("noninfected") within two groups by tabulating the following findings: (1) duration of diarrhea, (2) duration of parenteral fluid therapy, and (3) duration of hospitalization (Table VIII).

When comparing the "infected" and "noninfected" patients within each group, it will be observed that these features of our study reveal no significant difference. It is obvious that Aureomagma exerted a greater beneficial effect among the "noninfected" as well as the "infected" group.

Table VIII. Study of Patients With Positive Stool Cultures Versus Patients With Negative Stool Cultures

FINDING	PATIENTS WITH POSITIVE STOOL CULTURES		PATIENTS WITH NEGATIVE STOOL CULTURES	
	GROUP I	GROUP II	GROUP I	GROUP II
Average day of formed stool	5.3	4.4	5.2	4.1
Average days of parenteral fluid required	2.9	1.8	3.8	2.4
Average days of hospitalization	9.5	7.6	10.4	7.9

Aureomagma is effective in controlling diarrhea in infants and children due to *Sh. paradysenteriae,* and also is helpful in the control or prevention of secondary infection.

SUMMARY

The results of employing a combination of Aureomycin and triple sulfonamides—sulfadiazine, sulfamerazine, and sulfamethazine (Aureomagma)—are reported in the treatment of diarrhea of infancy and childhood. Diarrhea was due to infections with *Sh. paradysenteriae* or of unknown etiology. The combination has been evaluated according to the following criteria: (1) reversal of positive stool cultures, (2) influence upon the duration and severity of diarrhea, (3) requirement for extended parenteral fluid therapy, (4) reduction of fever, (5) length of hospitalization, (6) blood sulfonamide levels, and (7) undesirable side effects. In all respects, this combination was observed to be superior to a variety of chemotherapeutic and antibiotic agents when the remainder of the treatment was similar.

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CONDITIONS CLINICALLY CONFUSED WITH THE RHEUMATIC STATE

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RHEUMATIC FEVER and its cardiac complications so often fail to present a pathognomonic picture that this diagnosis has become a veritable wastebasket for illnesses whose signs and symptoms cannot be readily differentiated. This has become evident at our outpatient clinic, where for some time we have been observing an increasing number of referrals for the rheumatic state which on study and evaluation turned out to have conditions other than rheumatic.

Analysis of our records revealed 117 such cases. This is a report of the features which we believe led to their confusion with the rheumatic state and those which determined our final diagnoses.

TABLE I. DIAGNOSES IN 2,045 OUTPATIENTS

DIAGNOSIS	NO. OF CASES	PER CENT
"Rheumatic state"	481	23.5
Congenital heart disease	482	23.6
Coexistent rheumatic and congenital heart disease	8	0.4
No heart disease	957	46.8
Other conditions (originally suspected of being rheumatic)	117	5.7
Total	2,045	100.0

MATERIAL AND METHODS

Final diagnoses listed on the records of 2,045 patients were reviewed. Each patient had been referred to the clinic for cardiac evaluation by either a practicing physician, hospital, school physician, or social service agency. Every record consisted of a detailed history, physical examination, urinalysis, complete blood count, sedimentation rate, and findings on fluoroscopy, electrocardiography, and roentgenography. In general, the final diagnosis represented the opinion of three or more physicians of the hospital staff.

Criteria of the American Heart Association[1] were followed in diagnosing the rheumatic state and congenital heart disease. "Rheumatic state" included active and inactive rheumatic heart disease, active rheumatic fever, and a history of rheumatic fever without apparent cardiac involvement. Functional murmurs and the finding of a prominent pulmonary conus on roentgenogram, in the absence of other evidence corroborative of organic heart disease, were classified as no heart disease.

RESULTS

Table I groups the diagnoses in the 2,045 outpatient records. It can be seen that conditions originally suspected of being rheumatic but found

From the National Children's Cardiac Hospital.

TABLE II. 117 RHEUMATIC SUSPECTS: FINAL DIAGNOSES AND DIFFERENTIAL DIAGNOSTIC FEATURES

FINAL DIAGNOSIS (ACCORDING TO DISEASE GROUP)	NO. OF CASES	FEATURES CONFUSED WITH RHEUMATIC FEVER	DETERMINATIVE FEATURES
Blood Disorders (24 cases)			
Sickle-cell anemia	6	Heart murmur Cardiac enlargement Low-grade fever Joint pains	Sickling in blood smear Hemoglobin as low as 6.8 Gm.% *Diffuse* cardiac enlargement
Anemias due to parasitic infestations	5	Low-grade fever Fatigue Joint pains Weight loss Chest pain	Mild anemia (Hemoglobin 11.6 Gm.%) Eosinophilia 14% to 41% Positive stool specimen Larva migrans in one case
Anemia (unclassified)	10	Cardiac enlargement Heart murmur	Hemoglobin as low as 2.75 Gm.% Red blood cells as low as 2,150,000
Purpura (allergic)	1	Polyarthritis Low-grade fever	Ecchymoses Eosinophilia 12%
Splenic enlargement	2	Heart murmur Irregular heartbeat	Palpable spleen Generalized lymphadenopathy Anemia History of jaundice
Cardiac Disorders (5 cases) (Excluding congenital heart disease and functional murmurs)			
Arrhythmias	3	Heart murmur	Nodal rhythm on electrocardiogram (2 cases) Marked sinus arrhythmia on electrocardiogram (1 case)
Diphtheritic myocarditis	1	Muscle aches (growing pains)	Roentgenologic evidence of cardiac enlargement No history of rheumatic fever History of diphtheria in childhood
Acute benign pericarditis	1	Chest pain	Presence of acute unexplained pericarditis, with complete recovery on 2½-year follow-up
Endocrine and Nutritional Disorders (Thyroid dysfunction, 4 cases; calcium deficiency, 1 case; rickets, 1 case; unclassified, 1 case)	7	Tachycardia Heart murmur Frequent colds Joint pains	Hypertension Tachycardia B.M.R. + 50; response to thyroid medication Auricular extrasystoles on electrocardiogram "Potbelly" Anemia
Febrile Illnesses (13 cases)			
Tuberculosis	6	Low-grade fever Joint pains Chest pain Heart murmur Listlessness Weight Loss	Roengenologic evidence of pulmonary tuberculosis Pericardial fluid Cervical lymphadenopathy Positive tuberculin test Hemoptysis

(Continued on next page.)

TABLE II—CONT'D

FINAL DIAGNOSIS (ACCORDING TO DISEASE GROUP)	NO. OF CASES	FEATURES CONFUSED WITH RHEUMATIC FEVER	DETERMINATIVE FEATURES
Brucellosis	1	Frequent bouts of high fever	History of drinking raw milk
Cellulitis	1	Heart murmur	Cellulitis of hand
Dental caries	1	Mandibular joint pain	Marked dental caries
Acute suppurative adenitis	1	Low-grade fever	Tender, hard cervical glands
Fever of unknown origin	3	Intermittent fever	No symptoms other than fever
Neurological Disorders (6 cases)			
Epilepsy	4	Unconsciousness attributed to circulatory collapse	Episodic character of attacks Groaning Eye rolling Urinary incontinence
Brain tumor (verified by autopsy)	1	Cold, fever, migratory joint pains, tachycardia	Blindness No heart murmur Mass in right temporal region (on autopsy)
Poliomyelitis	1	Joint pains Low-grade fever	Headaches and dizziness Inability to straighten leg Presence of high incidence of poliomyelitis in community
Neuroses	16	Fatigue Heart murmur Chest pain Low-grade fever Malaise Joint pains	Marked concern about heart; consciousness of heartbeat Heart disease in parents Tachycardia; pounding of heart Fainting Tension; irritability; marked restlessness; nervousness Anorexia Personality changes; depression; temper tantrums Presence of family problems; school difficulties Headaches; migraine Nail biting; teeth grinding; nose picking; enuresis Phobias (dark, height, thunder, lightning) Neurodermatitis
Renal Disorders (Nephritis, 6 cases; pyelitis, 1 case)	7	Sore throat Fever Joint pains Heart murmur	Albuminuria, hematuria, low specific gravity of urine Hypertension Burning on urination "Red urine" following sulfa drugs Swollen feet, face, hands Anemia Headaches

(*Continued on next page.*)

TABLE II—CONT'D

FINAL DIAGNOSIS (ACCORDING TO DISEASE GROUP)	NO. OF CASES	FEATURES CONFUSED WITH RHEUMATIC FEVER	DETERMINATIVE FEATURES
Respiratory Conditions (33 cases)			
Infections (tonsillitis, bronchitis, bronchiectasis, sinusitis, pneumonia)	17	Joint pains Heart murmur Low-grade fever Leukocytosis Elevated sedimentation rate Recurrent colds Fatigue	Hypertrophied, congested, cryptic tonsils Rapid fall in sedimentation rate with improvement Congested nose; postnasal drip Cervical gland enlargement Recurrent pneumonia Diffuse or localized pulmonary râles Roentgenologic evidence of pulmonary infection Roentgenologic evidence of infiltration and fluid in antrum
Asthma (allergic)	12	Dyspnea Cough Heart murmur Recurrent fever Joint pains	History of attacks of wheezing Family history of asthma Seasonal rhinitis Expiratory râles and wheezes Roentgenologic evidence of peribronchial infiltration Eosinophilia
Rhinitis (allergic)	2	Frequent sore throat Joint pains Heart murmur Fatigue Fever	Perennial rhinitis with morning sneezing Chronic nasal discharge Frontal headaches Pharyngeal lymphoid hyperplasia
Mass in chest	2	Dyspnea, cyanosis Roentgenogram interpreted as cardiac enlargement Chest pain	Mass in right lower lobe found on roentgenogram (1 case) Constriction of superior vena cava found on roentgenogram (1 case)
Miscellaneous Conditions (6 cases)			
Cervical rib	1	Heart murmur	Hypertension in right arm Roentgenogram showed right cervical rib
Rheumatoid arthritis	4	Recurrent sore throats Joint pains Fever Elevated sedimentation rate Heart murmur	Multiple joint involvement Spindling of fingers Permanent joint damage
Rheumatoid arthritis with ulcerative colitis	1	Polyarthritis Elevated sedimentation rate	Recurrent, frothy, bloody diarrhea Roentgenologic evidence of ulceration of colon

to be otherwise were established in 117 patients.

Table II lists our final diagnoses in these patients, the features which probably caused their confusion with rheumatic fever, and those which determined our final diagnoses.

COMMENT

The finding of 5.7 per cent of patients with conditions confused with the rheumatic state emphasizes the need for a more discriminating approach to the problem of diagnosis of rheumatic fever. Actually, the per-

centage of those with nonrheumatic conditions is greater (19.3 per cent), if those with congenital or no heart disease are excluded. Furthermore, there would have been even more than 117 patients with nonrheumatic conditions had we attempted to follow all patients beyond consideration of their cardiac status. Once the presence or absence of organic heart disease was established, we no longer looked for other coexisting conditions. In the 117 patients, the nonrheumatic diagnosis was made in the course of the cardiac study.

In our discussion, we shall show how a careful history, the knowledge of differential diagnostic aids, and the proper use of laboratory tests may assist in ruling out rheumatic fever and arriving at accurate diagnoses.

Fever: The presence of chronic, low-grade fever, especially with a coexisting heart murmur, warrants the consideration of rheumatic fever. Tuberculosis, histoplasmosis, coccidioidomycosis, and similar pulmonary and systemic diseases, which may also produce this picture, should be excluded, and can usually be differentiated by roentgenograms and appropriate skin and blood tests. The teeth and gums should always be examined as their infection may produce fever. Local or generalized skin or lymphatic involvements similarly should be considered. Urinary tract infections, as a cause of persistent fever, are likely to be difficult to differentiate: intensive physical and laboratory studies may be required to establish their presence.

Joint pains, leukocytosis, and elevated sedimentation rate, in combination, also characterize rheumatoid arthritis. Differentiation is facilitated by the fact that frequently a markedly elevated sedimentation rate in rheumatoid arthritis occurs with mild symptoms, while in rheumatic fever it is usually associated with more active disease. Permanent joint damage is, of course, pathognomonic of rheumatoid arthritis, and often requires prolonged and frequent observation for accurate evaluation. Rheumatoid arthritis may be asociated with a nonspecific colitis. Patients with ulcerative colitis often show a rheumatoid-like syndrome. In one of our patients, rheumatoid arthritis was diagnosed, rather than rheumatic fever, when a history of repeated bouts of diarrhea, in association with joint pains, led to roentgenologic examination of the colon, revealing the presence of ulcerative colitis. Of course, in some instances, the symptoms of rheumatic fever and rheumatoid arthritis may be so similar that their differentiation is impossible.

Heart murmur: The presence of a murmur, without other stigmas of cardiac disease, should be interpreted with the utmost caution. The very fact that so many of our patients suspected of having heart disease were found to have functional murmurs, indicates that there is no cause for alarming a family nor risking the initiation of a cardiac neurosis in the patient. In informing parents of the existence of functional murmurs, it is essential to point out that there is no need for worry nor restriction of activity, such as commonly prevails when the word "murmur" is heard.

Other cardiac ailments may confuse the picture. In our series, congenital lesions were grouped apart from the 117 nonrheumatic conditions, and oc-

curred in 23.6 per cent of the entire series. There were many instances in which both rheumatic and congenital heart disease were confused with each other because of the similarity of murmurs, cardiac enlargement, and suggestive history.

The importance of a painstaking history cannot be stressed too often. It was only by careful questioning that we were able to discover a case of diphtheritic myocarditis, which on initial study was thought to be rheumatic heart disease. Prolonged observation also may be necessary in some cases to arrive at a final diagnosis. A case of acute benign pericarditis was differentiated from rheumatic heart disease when the initial illness was found to have resolved completely without any residua after two and a half years.

Neuropsychiatric factors also may produce cardiac symptoms, as evident in 16 of our patients. Most of these children had functional murmurs. Their cardiac complaints often stemmed from undue emphasis placed on these murmurs by physicians and parents.

Hypertension may occasionally arise from other than cardiovascular renal conditions. In one of our patients, unilateral hypertension was roentgenographically demonstrated to be due to a cervical rib on the same side. Bilateral cervical ribs could produce hypertension indistinguishable from that of cardiovascular origin.

Arrhythmia is a frequent presenting sign in cardiac suspects. It does not of itself constitute organic heart disease, and it has been our practice to consider as normal those hearts in which arrhythmia was the sole disturbance. Only three cases are tabulated because of their unusual nature: two had nodal rhythm proved by electrocardiogram, and one had marked sinus arrhythmia simulating atrial fibrillation.

Respiratory disorders are so often associated with fever, diffuse muscle aches and pains, and functional murmurs that they are commonly confused with rheumatic fever. Allergic asthma and rhinitis also may produce the same general rheumatic picture. A careful history, thorough study of the nose, throat, sinuses, and lungs, and therapeutic response to the antibiotics or antihistamines may help differentiate these conditions. In some cases, repeated follow-up examinations may be necessary.

Anemias: The triad of fever, joint pains, and murmur, synonymous with rheumatic fever, also may be caused by various types of anemia. Cardiac enlargement, tachycardia, and even cardiac insufficiency are common in anemia. Where functional murmurs are already present, mild degrees of anemia may accentuate them. If the anemia is severe enough, it, of itself, may produce a murmur. Therefore, in all cardiac suspects, blood studies are imperative to rule out anemia. A sickle-cell preparation is mandatory in every Negro child, because sicklemia often cannot be otherwise differentiated. The coexistence of sickle-cell anemia and rheumatic infection is so rare that the presence of sickling practically eliminates the rheumatic diagnosis.

Where parasitic infestations are the cause of anemia, the presence of eosinophilia, parasites or ova in the stools, or larva migrans in the skin may serve as differential clues.

It may often be necessary to perform further hematologic studies, such as determinations of bleeding and coagulation time, clot retraction, number of platelets, fragility, packed cell volume, mean corpuscular volume, and bone marrow biopsy, before the true cause of an anemia can be determined. Such tests will serve to differentiate rheumatic disease from dyserasias including purpura, pancytopenia, and others associated with splenic enlargement.

Renal disorders: Evidence is accumulating that glomerulonephritis, like rheumatic fever, may be causally related to Group A beta hemolytic streptococci. The two diseases may coexist. In fact, in the advanced stages, it may be impossible to determine which was the primary illness. Repeated urinalyses will help to establish the presence of glomerulonephritis. Pyelitis also may be detected by urinalysis, though on occasion renal function and catheterization studies may be necessary.

Endocrine and nutritional disorders are often associated with anemia, cardiac enlargement, arrhythmias, and murmurs. These should be borne in mind in the course of the physical examination and history, and if suspected should be ruled out by such tests as determination of the basal metabolic rate, protein bound iodine, blood calcium, phosphorus and phosphatase levels, and roentgenograms.

Neurological disorders: Four cases of epilepsy and one of brain tumor in our series were referred to us as possible rheumatic heart disease. In all these patients, the seizures were characterized by dyspnea and cyanosis which were attributed to circulatory insufficiency. The low-grade fever and muscle aches of poliomyelitis were interpreted as rheumatic infection in one case.

SUMMARY

Case records of 2,045 outpatients suspected of having rheumatic or congenital heart disease were reviewed. It was found that 46.8 per cent had no heart disease, 23.5 per cent were in the "rheumatic state," and 23.6 per cent had congenital lesions.

"Nonrheumatic" conditions, in which prolonged fever, joint pain, and heart murmur were part of the picture, were mistakenly diagnosed as rheumatic fever or rheumatic heart disease in 117 cases (5.7 per cent). The signs and symptoms which confused these conditions with the rheumatic state and those which determined the final diagnoses were tabulated and discussed, with special emphasis on methods of preventing such mistaken diagnoses.

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PAINLESS INJECTIONS IN PEDIATRIC PRACTICE

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THE pain of injections, however skillfully given, is a constant difficulty of pediatric practice, and a major obstacle to a pediatrician's establishment of good relations with his patients.

Several attempts have been made to solve this problem. The "Hypospray," depending on rapid high pressure injection, is painless, but the depth of injection cannot be regulated and injectables must be specially packaged for use in the apparatus. Mueller[1] recently reported his success with a cartridge containing Freon gas to cool the skin of the injection site to the point of temporary anesthesia. This is suitable for any transcutaneous injection, but requires special equipment.

I have found satisfactory a method using the same principle of skin cooling, but requiring no other equipment than a refrigerator. A 1:1,000 aqueous solution of Zephiran, with coloring material added for psychological effect, is poured into ordinary ice trays and frozen. (The antiseptic properties of the solution are unchanged by freezing.) Just before an injection, the chosen site is firmly rubbed with the ice cube until well chilled and temporarily anesthetized, and the injection given rapidly with a sharp needle.

I use this technique with all patients old enough to remember pain and fear injections, on all skin-puncturing procedures that do not require a dry field, such as vaccination, or immediate free flow of blood, such as bleeding time determinations. The temporary anesthesia is cutaneous only, and without effect on subsequent pain and stiffness, or the pain of injection of large volumes of solution. However, the psychological reaction to piercing the skin is eliminated, as shown by the relieved laughter of older children who tell their mothers, "It didn't hurt," and return without fear for later injections.

It is hoped that this simple method will prove useful to those who wish to spare their patients pain.

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TRAINING PROGRAMS IN SCHOOL HEALTH SERVICE

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THE general tendency in school health service is away from the routine annual health examination of pupils. There are many reasons why this is so, not the least among them being that many school physicians seriously doubt the efficacy of attempting to single out those who require medical follow-up of significant defects found on a mass basis. No one questions the desirability of a thorough annual physical check-up with parents present and a sound follow-up program of health problems discovered. In practice, however, it is well known that this situation does not obtain. The reasons are many but principal among them are lack of qualified medical and nursing personnel and lack of adequate budgetary appropriations. The problem of supplying a school health service is a complex one and because of this there is a variety of state and local laws on the subject concerned mainly with the number of examinations to be done within the elementary school period.

There is a growing tendency to regard the finding and following of the child with a health problem as the primary objective of school health service, with a decreasing emphasis on the periodicity of routine examinations. The Astoria School Health Study is an example of this.[1, 2, 3, 4] It has been emphasized, and requires repeated emphasis, that programs based on this premise must have the following minimal attributes to operate successfully:

1. Physicians well trained in school health practice.
2. Public health nurses with special orientation in school health service.
3. Teachers with training in pupil health observation.

While it may appear to be stating the obvious, a little inquiry into school health service programs in the United States will disclose that the above requirements are not easily met, and because of a deficiency in any one of the three, the program suffers.

Recognizing these facts, efforts have been made in New York City in the past several years to develop a teaching program which would give the school physician the basic understanding of the principles of school health service in a practically useful fashion. One may ask what special qualifications are required of a school physician which the average physician does not possess. It may be assumed that in most instances he is a general practitioner who includes care of children as part of his regular activities. Three things appear to stand out to warrant extra time being spent in training for the school physician. First, the vast majority of pupils he will see are presumably well children.

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They do not come to the medical room with complaints; rather they and their parents usually present themselves because of legal requirements. Thus instead of seeking the cause for a complaint, the school doctor must discover and evaluate deviations or potential deviations from the normal. In short, it may be said the examination is health—rather than disease-centered. Therefore, the kind of things looked for, the history taking, and above all the advice given a parent will have many implications as to the future health care of the child, particularly as his development, emotional and physical, is affected by attendance at school. Second, the school physician must be familiar with screening techniques such as vision and hearing and be able to evaluate the results of such tests for the educational staff. He gets relatively little of this experience in private practice. Third, he must be familiar not only with the school environment, physical plant, and sanitary equipment with respect to their over-all effect on school children, but must be thoroughly familiar with the many kinds of physical education programs, directed and otherwise, encountered in the day-to-day activities of the child.

The subject of school environment and physical activities has many complex ramifications. The question of special class placement for the handicapped, the limitations of physical activities for the debilitated child, the routine examinations for competitive sports, in fact the definition of competitive sports, all of these come at one time or another to the school physicians for solution. That these subjects require special knowledge is manifest by the not infrequently ill-advised restrictions placed on a child by the family physician who does not have an over-all familiarity with the school. Therefore, the goal in orientation must be to inculcate a public health attitude to the health problems of the school age child while at the same time retaining the individual contact with the parent and child, a skill which he already has to a high degree. This must never be dropped in school health practice but the public health implication, the knowledge of school and community resources, must be inculcated if the physician is to be successfully oriented in school health service. Many of the clinical problems when examined from the point of view of the school environment will appear much broader in their implications than when seen purely as a clinical entity per se for which simple medication may be prescribed. For example, the child with rheumatic heart disease may present a relatively clear picture from the point of view of hospital treatment, medication, and recreation, but how should he be handled when he is ready to return to school. Recommendations may be made by the treatment agency as to limitation of activity. How and to what degree can this be arranged and supervised? Who shall see that follow-up of the case is carried out? It is clear from these questions that the school doctor and nurse must of necessity become involved in the health supervision of such a child attending school. There will be communication with the child's doctor or treatment agency, the classroom teacher, the handicapped class teacher, and the parent to ensure the proper interpretation of the treatment agency's recommendations to the teaching staff. So it has become in-

creasingly clear that for a school health service program to function well the physician must have sound orientation before he starts. It has been found entirely feasible to develop such an orientation program at relatively little public expense. Moreover, it has been demonstrated that such a program is readily accepted by the physician. The reasons for this will be apparent as the program is described.

Experience indicates that it takes about five to six weeks (five three-hour sessions per week) to cover the ground. Obviously the program makes no claim to teach the physician clinical medicine. Rather, as the name implies, it attempts to orient medical knowledge and experience already acquired, to the health supervision of the child at school and, in addition, acquaint him with the school as a dynamic organism. The orientation course is divided into two major parts (see Table I).

1. Lecture, demonstration, and conference periods.
2. Field observation and actual participation in work.

The subjects covered in Part 1 include instruction in:

1. Functions of the physician, nurse, and teacher in school health service with formal demonstration of history taking, physical examination, and parent-doctor conference as performed in the school medical room.
2. Normal physical and emotional growth and development and the influence of the school environment.
3. The educational placement of the physically handicapped child including the cerebral palsied.
4. The educational placement of the emotionally and mentally handicapped child.
5. Communicable diseases of childhood and their relation to school attendance.
6. The school dental program.
7. Health and physical education programs in the schools.
8. Administrative aspects and technical instructions.

The faculty is drawn from the Department of Health, Board of Education, and medical schools in the city. The method of teaching is by lecture and conference—informal in character, always with ample opportunity for the physician to comment or ask questions. In addition, four review sessions are provided at appropriate intervals at which the trainee has complete freedom for discussion, questions, and comment. Experience indicates that these review sessions are of the greatest value in assisting the physician in gaining a clear and broad understanding of school health practice. Moreover, because they provide opportunity for fresh unrestricted critical appraisal of the service as seen by the newly appointed physician, they are invaluable to the staff in administering the program and in modifying the course so as to more accurately supply the needs of the new physician in the field. The doctor is made to feel that he is a part of the service.

In Part 2 of the teaching program, the physician actually does the work of the doctor in the school. He is supervised directly by the physician regularly assigned to the school. In this way he becomes thoroughly familiar with field practice, learns the use of forms, how to refer, relationships with education staff and many other features of school health service which can only be learned by practice, however much preliminary indoctrination is given. Following the course, after a school physician has been on regular assignment for about four months, occasional review sessions are

again held to determine how effective training has been and to receive further suggestions as to future conduct of the course.

For the past five years, two such courses per year have been given. The larger group. There has been a 10 to 20 per cent turnover in medical personnel per year during the five-year period, and 160 physicians have attended the course in all. Unsolicited comment from school personnel and

TABLE I. TRAINING PROGRAMS, BUREAU OF SCHOOL HEALTH, SCHOOL HEALTH SERVICE, DEPARTMENT OF HEALTH, NEW YORK CITY

PHYSICIAN'S PRESERVICE COURSE

Session—3 hours each:	
1. Historical Development General Administration	Professor of Public Health, Cornell Director, Bureau of School Health
2. Function of School Physician	Consultant, School Health (Assistant Professor of Cornell)
3. Function of Nurse	Consultant, Bureau of Nursing
4. Function of Teacher	Assistant Superintendent, Board of Education
5. Demonstration—Class Room Parent conference and examination of pupils (elementary)	Supervising Physician, School Health
6. Health Service—Secondary Schools	Supervising Physician, Department of Health
7. Field Observation Elementary and Secondary Schools	Principals, Board of Education Supervising Physicians, Department of Health
8. Review	Staff
9. Normal Growth and Development—physical, school age through adolescence	Associate Professor of Pediatrics, New York University and Bellevue Medical Center
10. Emotional Development—school age through adolescence Functions of Bureau of Child Guidance	Child Psychiatrist, Board of Education Psychologist, Board of Education
11. Communicable Diseases, prevention and control	Director, Bureau of Preventable Diseases, Department of Health
12. School Dental Health Program	Director, Bureau of Dentistry, Department of Health
13. Handicapped Child of School Age and His Problems	Director, Bureau for Handicapped, Department of Health
14. Common Handicaps: Educational Placement Cardiac	 Consultant Cardiologist, Department of Health
Orthopedic Cerebral palsy	Consultant Orthopedist, Department of Health Consultant Orthopedist, Department of Health
15. Common Handicaps: Educational Placement Visual	 Consultant Ophthalmologist, Department of Health
Auditory	Consultant Otologist, Department of Health
16. Epilepsy in School-Age Child Mental Retardation Program Elementary Schools	Child Psychiatrist, Board of Education Supervisor, Board of Education
17. Review	Teaching Staff
18. Working Paper Clinics	Supervising Physician, Department of Health
19 to 31. Field assignments to Elementary and Secondary Schools and Working Paper Clinics	Supervising Physicians, Department of Health School Physicians, Department of Health
32. Review	Teaching Staff

average number of physicians attending is fifteen to twenty per course. Larger numbers are not desirable since informal free discussion cannot be carried out advantageously with the district health officers unanimously indorse the course as producing a superior type of school health physician. The doctors themselves frequently remark that the material

learned and experience obtained in the school health service have been helpful to them in their private practices in dealing with parents and children.

Even with the experience thus far gained in presenting a course of this nature, it is not felt that the ultimate has been reached. For during the short span of five years, emphases and priorities in school health service[6] have changed. Such genuine changes as occur must necessarily be reflected in the course content. There is no doubt, however, that this approach to the improvement in quality of school health practice is sound and pays generous dividends in better health service to children of school age.

TEACHER OBSERVATION PROGRAM

Repeatedly, to the point of monotony, it has been stated that the classroom teacher is the "key person" in a school health service program, meaning, of course, that by her keen clinical observation of "health behavior" in the classroom she is able to discover the child presenting a health problem either acute or less obvious. While there can be little argument that such a situation is highly desirable one may reasonably inquire as to how effectively the teacher with her increasing responsibilities in educational work has the time, inclination, or theoretical ability to perform such screening observations. Where does the newly appointed teacher have the opportunity to learn how to observe and judge a child's health behavior? It is true that with the passing years many teachers do acquire a knack of spotting the child with health deviations but it is probably also true that many do not. It would seem that if the teacher had some direct contact with the health service in her school she would learn of its advantages and limitations and with her interest aroused thus be in a position to use it intelligently in making appropriate referrals to the nurse or physician. With this thought in mind a rather simple program was developed whereby student teachers entering their final year of training would have an opportunity to learn the fundamentals of school health service. It has been received enthusiastically by the colleges* and is now entering its fourth year of operation.

Briefly the program is as follows:

Just prior to the assignment of the fourth year student teachers to field work in the public schools throughout New York City and adjacent counties they attend a two-hour conference at which full-time members of the Bureaus of School Health and Nursing present the salient features of the health service as they relate to the classroom teacher. It is essentially an orientation in the general subject of health observation of the school pupil, the part the school physician and nurse have, and the teacher's role in health supervision. Provision is then made so that at some point during her field assignment the student teacher observes one doctor's session and one teacher-nurse classroom conference. Upon completion of her field work and return to the college, a two-hour review session is held again with the Department of Health staff who gave the original orientation. All in all the program takes about nine to ten hours. It is well integrated into the curriculum of the student so that no incon-

*Programs now in operation at College of the City of New York, Hunter College, and Queens College.

venience is encountered. During the three years that the program has been operating, more than 1,000 student teachers have had the course. Simple and brief though it is, a remarkable amount of solid information appears to have been gained by the students from this experience. This is evident particularly by the kinds of questions asked and comments of the students when they attend the review sessions. It can reasonably be expected that when they take up their assignments as teachers they will at least have an awareness of what the school health service is and of their own part in the program. One may modestly suggest that more experience of this kind when made available to student teachers will, in the long run, truly produce the "key person" in the school health program.

MEDICAL STUDENT TEACHING

Over the past twenty-five years there has occurred a marked change in the medical school curricula both as to methods of teaching and content material. The ever-broadening field of public health has shared in this change. New topics have been introduced into the undergraduate medical curricula as their importance became manifest while some of the older ones were dropped. Recognizing that the health of the school-age child was a matter of increasing concern, the subject has been included as part of public health teaching by the five medical schools* of New York City. A similar program has recently been reported at the University of Washington.[7] As in the program for student teachers, the course here is short and concise with the purpose of familiarizing the medical student with the major objectives and practices of a school health service. The students are given preliminary orientation in the subject by one lecture or conference followed by direct observation of a medical session at the schools. Subsequent review is carried on at the medical schools often in connection with related subjects in the field of maternal and child hygiene. It is a cooperative activity shared in by the Professors of Public Health at the medical schools, the physicians of the Bureau of School Health and district health officers. While no claim could be made to orient him fully in school health, the student does learn basic facts which will be useful to him later on in practice and at the same time be advantageous to school educational and medical staff.

SEMINARS AND CONFERENCES FOR SCHOOL PHYSICIANS

While in-service training programs give us assurance of efficient school physicians, it has been found advantageous to make available to them seminars on topics of current interest which they may attend on a voluntary basis. This usually takes the form of six to eight two-hour sessions consisting of lectures followed by discussion periods. For the past two years the emotional development and behavior patterns of school children have been the center of interest so that seminars on this topic have been held each year. Prior to that, physical growth and development of the school-age child was presented. We were fortunate in having eminent specialists with the know-how of teaching to conduct these seminars. The presentation of one broad

*College of Physicians and Surgeons, Columbia University; New York University-Bellevue Medical Center; Cornell Medical College, New York Medical College, and New York State College of Medicine.

subject in continuity seems to be more attractive to school physicians than a series of lectures on unrelated topics. However, occasions arise when briefing on immediate problems must be given. For example, it was necessary about two years ago to give a short series of lectures on narcotic usage among students as one part of a program developed to attack this problem.[8] While these seminars help to sustain interest in school health service they are not in themselves sufficient to guarantee the best in school health practice. A notably useful device to give the individual physician a personal interest in his work is to have regular monthly meetings of local groups of school physicians at which they present cases of medical and public health interest which they encounter in the school medical room. The subject matter for discussion is determined by the physicians themselves, the only limiting feature being that it pertains in some fashion to solving health problems of the school-age child. Often they invite a specialist in an appropriate medical subject to participate.

TABLE II. TRAINING PROGRAMS, SCHOOL HEALTH SERVICE, BUREAU OF SCHOOL HEALTH DEPARTMENT OF HEALTH

		NO. OF SESSIONS	HR./SESSION
1. Student	Medical—conference-observation-review	4	2
	Teacher—conference-observation-review	4	2
2. In-service	School Physician—training program—6 weeks	32	3
	Child and School Health Physicians—lecture courses, early childhood through adolescence	8	2
3. Graduate	Columbia School of Public Health students—theory and practice of school health, including field observation for physicians, nurses, public health educators, health officers, etc.	8	3

GRADUATE SCHOOL HEALTH COURSE

At the School of Public Health, Columbia University, a course in school health service theory and practice staffed by members of the Bureau of School Health is given yearly. Those attending, a widely varied group consisting of nurses, physicians, dentists, public health educators, health officers, etc., are regularly scheduled to observe both the elementary and secondary health programs in the schools as part of the course. The aims and content of this course are of necessity different from that for newly appointed school physicians but the broad general principles of a school health service program are included in both. (See Table II.)

SUMMARY

Instructional and training programs in theory and practice of school health service, elementary and secondary, have been described. The programs are adapted to the needs and time available for personnel concerned, namely, the student teacher, the medical student, the newly employed school physician, and the graduate public health student. The training of the public health nurse in school health service, obviously of the greatest importance, has not been included in this paper since it will be described

elsewhere. It is part of an over-all six-month in-service training given to all newly appointed nurses.

It will thus be seen that for a well-rounded instructional or orientation course in school health service with a view to the future as well as to immediate needs, not only the newly employed physician, but the future schoolteacher, the medical student, and the public health nurse must be grounded in at least basic understanding of its purpose and importance in the community. It is only by patiently laying the groundwork that finally a sound and effective school health service program can be attained.

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CHILD CARE IN UGANDA AND THE BELGIAN CONGO

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UGANDA, a British protectorate, is situated in the east-central part of Africa. Together with Kenya and Tanganyika on which it abuts, and Zanzibar, a coral island, it makes up the area known as British East Africa (Fig. 1). The population consists of approximately 5,000,000 Africans, 5,000 Europeans, principally British, and 50,000 Indians. The Africans are gentle, quiet, unaggressive, and easy-going. An interesting feature, pointed out by Dr. Hugh Trowell, specialist physician, Uganda Medical Service in Kampala, is the frequent similarity in body configuration and hair distribution of the sexes, an observation which has also been made for the American Negro. Men have little hair on the body, the pubic hair is often transversely limited above as in the female, and baldness is rare. The women have short hair on the head, and narrow pelves, often showing android tendencies and configuration.

The birth rate is high but childbearing often ceases after 30 years of age. Women generally marry at 18 to 22 years, men at about four years older. Women have their first child at about 19 to 23 years of age. Sex interest is often low. Homosexuality is extremely rare.

The average weight at birth is lower than that of white American children (average 3.04 kilograms for first-born males, average for white American first-born males 3.38 kilograms, average for Negro American males, all parities, 3.10 kilograms.). A considerable proportion of the newborn infants weigh less than 2.5 kilograms but the small ones generally do well and presumably many of these are full term. Breast feeding is practiced universally.

Although the mothers are not demonstrative they are affectionate and keep their babies in close contact with their own bodies. Child care is permissive and discipline is almost nonexistent. Little effort is made at toilet training until the child can walk. Babies are nursed until they are about 18 months to 2 years of age. At weaning, the baby is separated from the mother and turned over to the grandmother. At this time the mother often absents herself completely from her baby with the thought that this will facilitate weaning. Unlike the adults, the children are active and animated and play much like American children.

Exact data are unobtainable but the childhood death rate is extremely high. Trowell estimates that only about six out of ten children survive to the age of 5 years and probably less than half to adult life. The most frequent causes of death are nutritional disturbances, untreated respiratory infections, complications of measles and whooping cough, and malaria.

Malaria is common in children and is seen even in infants. Though gen-

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erally mild it is sometimes severe and the death rate in infants is considerable. Those who recover carry permanent immunity against the severer manifestations of the disease. Hookworm infestation is widespread, but is not often accompanied by severe anemia.

As among Negroes elsewhere scarlet fever is rare, but measles, whooping cough, chicken pox, and mumps are as common as in other groups.

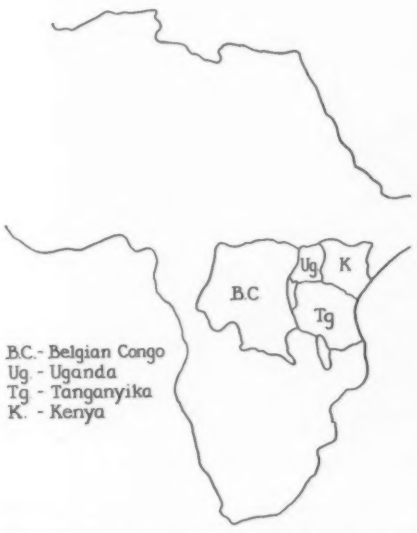

Fig. 1.—Map of Africa showing British East Africa and the Belgian Congo.

Congenital anomalies are less frequent than in the white population. Though syphilis is rife among the adults, congenital syphilis is uncommon in infants and appears to run a mild course.

According to Allison, sicklemia is present in about 19 per cent of the Baganda tribe. Sickle-cell anemia is not uncommon and probably occurs in about 1 per cent of Baganda babies.

Enuresis is observed in children and even among the students at the University. Among the Zulus in South Africa a favored method of treatment is to make incisions in the face and trunk to let out the "bad blood." The incidence of appendicitis and allergic disease is very low, as is that of acute rheumatism and chorea.

The Mulago Hospital.—There were about twenty-five African children in the ward at Mulago Hospital, Kampala, when I visited it early in August, 1953 (Fig. 2). The ward is part of the Uganda Medical Department and the Makere University Hospital. It is staffed by British physicians of the University faculty, assisted by African physicians. Makere University is for all races in British East Africa but at present the students are almost entirely African. The faculty is British. The children's ward is under the direction of Dr. Hugh Trowell whose duties include the medical care of adults as well. In addition to the regular staff, investigators are sent out from England to carry on special studies. At present Dr. R. A. F. Dean is at Kampala studying kwashiorkor, and Dr. Allison is studying sickle-cell anemia.

The service is adequately equipped to carry out the routine urinary, hematologic, chemical, bacteriologic, and x-ray examinations, all of which are under the direction of European physicians assisted by African physicians and technicians.

Nursing is done by African girls under the direction of an English supervisor or Sister, Miss E. Dentith. The African girls are conscientious, interested, good-natured but, with rare exceptions, entirely lacking in initiative.

Mothers, sometimes grandmothers, stay in the hospital with the children. They remain at the bedside during the day and sleep on the floor alongside the beds at night. The hospital supplies their food. No African mother in Uganda would allow her child into the hospital unless she could be with him. The mothers supply all care except giving medications, assisting at treatments and

Fig. 2.—Children's Ward, Mulago Hospital Kampala, Uganda.

the like. Occasionally sick orphans are admitted. Almost all of these die if they stay long in the hospital, so that efforts are made to get them adopted.

The illnesses from which the patients were suffering when I visited the ward were kwashiorkor (six cases), malaria, sickle-cell anemia, tuberculosis, nephritis (probably mixed), undernutrition, hookworm, suppurative arthritis (salmonella).

Kwashiorkor.—Kwashiorkor (Figs. 3 and 4) is a severe nutritional disturbance of early childhood. The disease was first described by Dr. Cicely Williams in 1933 in native children of the Gold Coast and since then has been recognized by others throughout tropical Africa, in certain regions of America, and in Asia. The "Mehlnährschaden" widely discussed in the German literature of two or three decades ago is probably the same disease. The onset in Uganda is usually in the second or third years of life, from a few weeks to several months following weaning from the breast. It is occasionally seen during the first year when, because of pregnancy or illness or other reason, the mother stops breast feeding or has little breast milk. It is rare during breast feeding. The principal symptoms are edema, frequent watery stools containing undigested food particles, undernutrition, skin lesions, brown, soft, scanty hair. The appetite is generally poor.

Prominent and constant in kwashiorkor are the psychologic changes. The children are dull, apathetic, and miserable (Clark). They rarely cry

or scream but show their unhappiness instead by whimpering. The African child, fearing the European physician, generally resists examination actively. Not so the child with kwashiorkor. His apathy is so great that he submits without any show of fight. He moves very little and, when placed in one position will remain there a long time. He is often irritable when disturbed. Trowell (personal communication) says that "if you see a child smile, he hasn't kwashiorkor." The changes in behavior and emotional response are among the most striking evidences of cure in kwashiorkor.

Kwashiorkor is probably, basically, a protein deficiency disease which may be associated with other deficiencies. Tropical infections are also usually present. Treatment by feeding skimmed milk has reduced the mortality from about 60 to about 15 per cent.

Trowell is of the opinion that a large proportion of African children in the second and third years of life show signs of mild kwashiorkor. They are underweight, the hair is

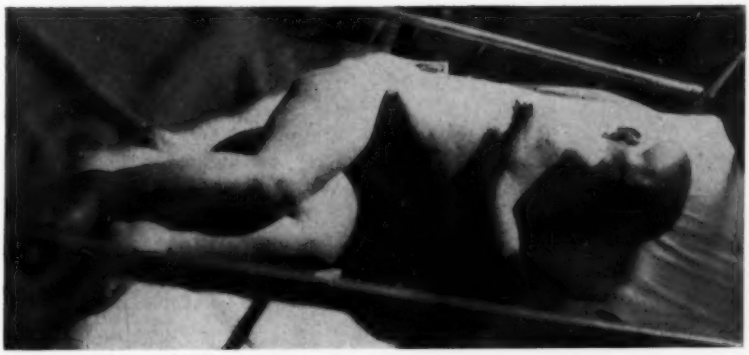

Fig. 3.—Child with kwashiorkor, showing marked edema.

Fig. 4.—Child convalescing from kwashiorkor. The child shows well the emaciation, the generalized skin depigmentation, and the hair changes.

brown and soft, instead of jet-black and firm, and the serum albumin is reduced. When treated as for kwashiorkor with skimmed milk, these changes return to normal.

Fig. 5.—Kisenyi, Belgian Congo. Native women with their babies at the Baby Health Station.

Fig. 6.—Kisenyi, Belgian Congo. African assistant at Baby Health Station.

BELGIAN CONGO

An active public health program is under way in the Belgian Congo. Health stations (Figs. 5 and 6) have been set up where the babies are weighed, feeding advice offered, inoculations against diphtheria and tetanus given, and vitamins dispensed. The women appreciate the value of these clinics and attend them conscientiously. The work is carried out by African assistants under the direction of European physicians.

A baby health session in Ruanda-Urundi where we visited is an animated spectacle. The women wait in informal cues, standing or lolling on the ground in the warm sun, chattering and laughing, their babies on their backs or in their arms suckling at the breast. The costumes are gay and bright colored, but the skimpy bodices would be hardly acceptable in Western society. A group apart are the tall, graceful, dignified Wa-

tussi women, draped in white like the ancient Greeks, the woolly hair atop their small heads elaborately dressed.

Outstanding work is being done by Dr. Carl Becker of Pennsylvania at the American Interdenominational Mission clinic in Oicha. Among many ill patients whom we saw at his hospital were several hundred lepers. Dr. Becker's work is widely appreciated all over East Africa and even in South Africa.

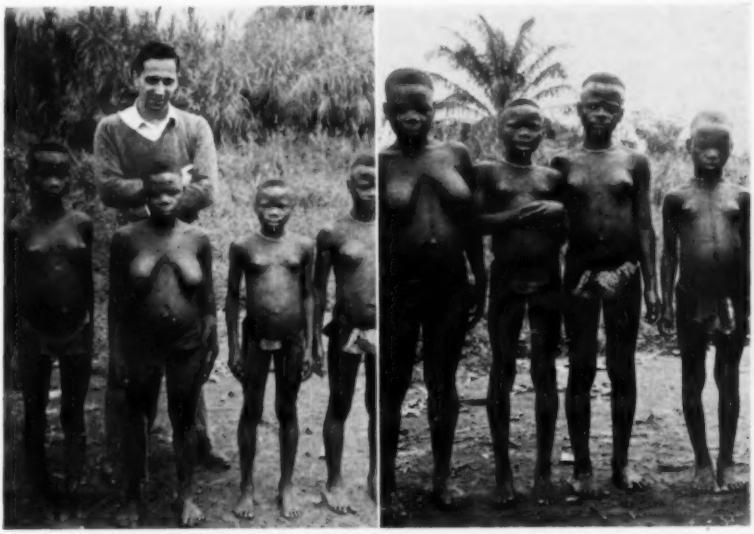

Fig. 7.—Pygmies of the Ituri Forest.

Pygmies.—The pygmies (Fig. 7) of the Belgian Congo are concentrated in the Ituri region, a dense forest plentifully supplied with rain for ten months of the year. Here the pygmies live under the forest trees and maintain an almost symbiotic relation with the Negroes whom they supply with meat and honey, in return for which they receive bananas, ax blades, knives, and arrowheads. The Negroes look down upon the pygmies whom they regard as a species apart. Though Negro men may marry pygmy women, Negro women never marry pygmies.

The pygmies live in tiny huts under the trees. They wear no clothes, only loin cloths. Their villages which consist of about 150 persons are temporary. They move frequently, generally staying only two or three months in a place. They move because, by that time, the game will have been frightened away. Moreover, the camp will have become malodorous, even by pygmy standards, from human refuse.

Children are greatly desired by the pygmies and are treated with care and affection. A childless marriage often leads to separation. According to Dr. Boris Adé (loc. cit.) the mean weight of pygmy babies at birth is 1.7 kilograms. Babies are nursed for about two years during which time the parents abstain from coitus. Twin births are said to be rare. It is customary to

do away with the weaker one. Deformed children are treated similarly.

Shortly after birth the infant is wrapped in soft fiber napkins made from leaves. After several weeks the elbows and knees are wrapped in

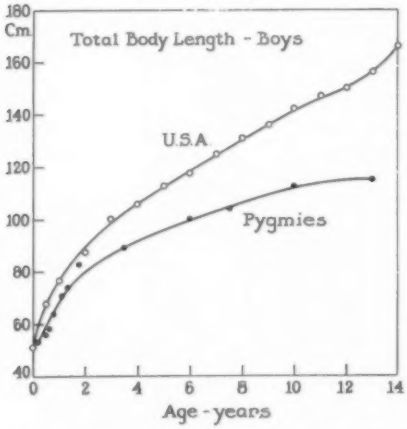

Fig. 8.—Growth in height of pygmy boys.

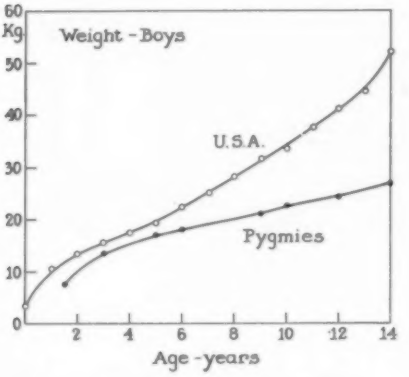

Fig. 9.—Growth in weight of pygmy boys.

bandages which are believed to strengthen the joints. The bandages are kept on until walking is well established.

Protrusion of the navel is frequent. Bowlegs are also common but they generally correct themselves. Common illnesses among the children are yaws, ophthalmia, and fevers. Clinical syphilis is rare. The death rate is high.

Growth curves of pygmy boys from 10 weeks to 13 years are compared with similar data on American boys (Bakwin and Bakwin, unpublished data) in Figs. 8 and 9. Body size measurements of newborn pygmies are not available, but it would appear that they are not a great deal smaller than American children at birth. Pygmy boys lag behind American boys at every age level. The discrepancy increases sharply after the sixth year. The pygmy boys fail to show an adolescent growth spurt. Similar differences are shown by the pygmy girls. Data on pygmies are of questionable reliability because ages are not known with any accuracy.

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MUCORMYCOSIS OF THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH THROMBOSIS OF THE INTERNAL CAROTID ARTERY

CAPTAIN FRANCIS P. MARTIN, MAJOR JOHN M. LUKEMAN, CAPTAIN ROBERT F. RANSON, AND LIEUTENANT COLONEL LEO J. GEPPERT, MEDICAL CORPS, UNITED STATES ARMY

A REVIEW of the medical literature revealed no recorded cases of mucormycosis of the central nervous system in infancy. There have been six cases recorded in adults.[1, 2, 3, 4] Five of these were in diabetics. Equally rare in infancy is carotid artery thrombosis. Of the fifty-two reported cases of arterial thrombosis in infancy, only two involved the carotid artery.[5] Because if its rarity and interest, the following case is presented.

CASE REPORT

A 2½-month-old white male infant was admitted to the Pediatric Service of Brooke Army Hospital on July 31, 1951, because of swelling of the left eye of four days' duration. Approximately two weeks prior to this admission the child developed diarrhea and was admitted to a private hospital where he was treated with chemotherapy and parenteral fluids. After several days of treatment, swelling of the left eye was noted and he was transferred to Brooke Army Hospital. The child was born of a normal spontaneous delivery following an uneventful pregnancy. His birth weight was 6 pounds 8 ounces. He was fed an evaporated milk formula with vitamin supplements. Developmental history was normal. The mother had congenital syphilis but was adequately treated prior to the birth of this child. The remainder of the family history was not significant.

From the Pediatric and Laboratory Services, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

Physical examination on admission revealed an extremely dehydrated, marasmic 2½-month-old infant with obvious swelling of the left orbit and the left side of the face. The temperature was 101.6° F., pulse 140 per minute, and respirations 40 per minute. The left orbit was swollen and ecchymotic. The eyelids were markedly edematous. The cornea was clouded and the fundus could not be visualized. The right eye appeared normal. There was a hard mass approximately 5 cm. in length and 3 cm. in width occupying the left side of the face. Except for the previously mentioned dehydration, the remaining physical findings were within normal limits.

Laboratory data on admission revealed a white blood cell count of 43,250 with a marked shift to the left. The hemoglobin was 5.5 grams. There were 11 nucleated red blood cells per 100 white blood cells. The carbon-dioxide combining power was 13 meq. per liter with serum chlorides of 122 meq. per liter. A lumbar puncture was performed revealing a clear fluid, normal pressure, and Queckenstedt's test. The spinal fluid sugar was 136 mg. per cent, the chlorides 650 mg. per cent, and the total protein 208 mg. per cent. Blood, spinal fluid, and stool cultures were negative for pathogenic organisms. Culture of nasal discharges revealed occasional pseudomonas-like organisms. Cultures for fungi were not done. X-rays of the chest, skull, abdomen, and sinuses revealed no abnormal findings.

Parenteral fluids, blood, and electrolytes were administered. One million units of penicillin and 0.5 Gm. of

streptomycin were given intravenously in the first twelve hours. These were followed by 100 mg. of streptomycin every twelve hours, and 200,000 units of penicillin every three hours. When no apparent effect was observed after forty-eight hours, penicillin was discontinued and intravenous Chloromycetin and sulfadiazine were added to the regime. He became hydrated and the serum electrolytes returned to normal (sodium 137.5 meq. per liter, potassium 5.3 meq. per liter, and chloride 99.8 meq. per liter). The red blood count and hemoglobin approached normal.

critically ill. He had several convulsions. The respiratory obstruction became more severe and his general condition failed to improve. Finally on the evening of the fourth hospital day, he expired. An autopsy was performed approximately thirteen hours after death.

Autopsy Findings.—The skin covering the left side of the face was gangrenous. The underlying buccal fat pad was indurated and swollen. The contents of the left orbit including the globe were necrotic. The orbital surface of the left frontal lobe was necrotic. There was a laminated

Fig. 1.—Face of patient showing gangrene of left side and swelling of eye twenty-four hours prior to death.

Despite therapy the swelling of the orbit and face became more pronounced. First the left side of the head and then the entire head became edematous (Fig. 1). The pharynx and tongue also became edematous, causing respiratory obstruction which was relieved by a rubber pharyngeal airway. On the third hospital day the left side of the cheek showed beginning gangrene. The gangrenous area spread rapidly to include the entire left side of the face. In spite of continued therapy, the child remained

thrombus of the left internal carotid artery extending into the left ophthalmic artery (Fig. 2). The eosphageal mucosa was ulcerated. There were a few areas of fibrinous pleuritis and the lungs were moderately edematous. The remainder of the gross examination was not significant.

Microscopic examination revealed extensive necrosis and an intense inflammatory reaction in all the involved tissues. Particularly prominent in these tissues were thromboses and inflammation of blood vessels.

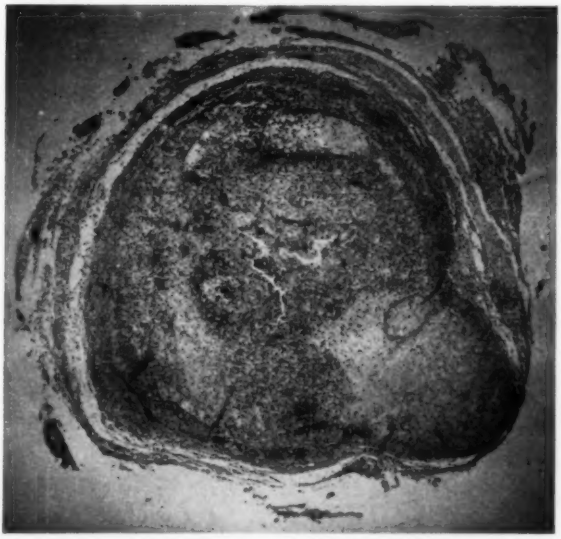

Fig. 2.—Cross section of left internal carotid artery at level of ophthalmic artery, showing thrombus. (H & E, ×40.)

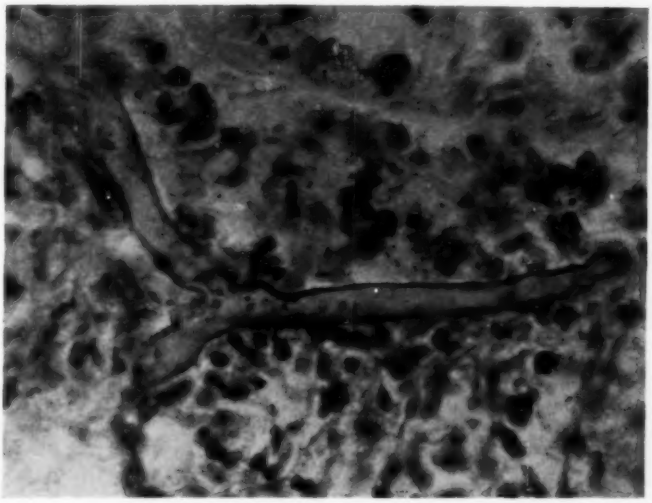

Fig. 3.—Section of internal carotid artery wall containing nonseptate branching hypha. (H & E, ×970, reduced ⅙.)

Innumerable large nonseptate hyphae were found in all the involved tissues as well as in most of the other organs (Fig. 3). These organisms showed an affinity for blood vessels, invading their walls and not infrequently occluding their lumina (Fig. 4). The walls of the thrombosed internal carotid artery were heavily invaded by these organisms. Hyphae were also observed in large numbers in the left globe and orbit, the left side of the face and its underlying tissues, the meninges, the esophagus, the pleura, the lungs, the pancreas, and the bone marrow. In all these organs the affinity for blood vessels was quite apparent. These hyphae were 100 to 200 microns in length and 10 to 20 microns in diameter. They demonstrated the morphology of the mucor species as described by other authors.[1, 2, 3, 4, 6] Cultures for fungi were not obtained.

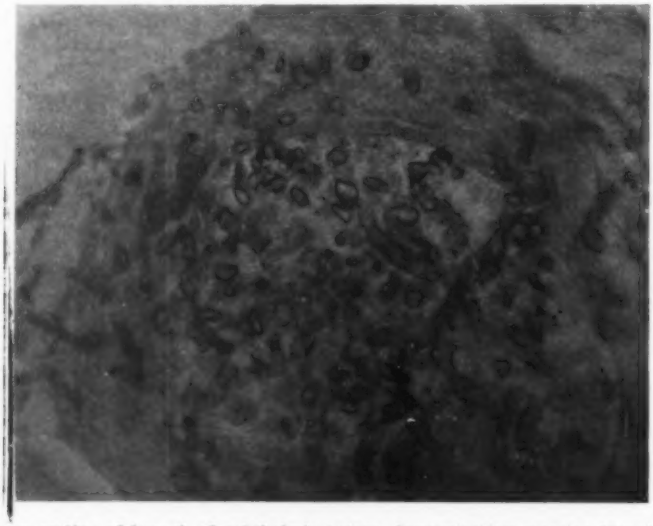

Fig. 4.—Cross section of branch of ophthalmic artery, demonstrating massive invasion of walls and lumen of the vessel. (H & E, ×470, reduced ⅙.)

COMMENT

The mucor species is a nonseptate vegetative mycelium of the class Phycomycetes. It gives rise to numerous sporangiophores of unequalled length which branch irregularly and bear terminal sporangia.[7] These sporangia are produced only in the walls of the bronchi where oxygen is abundant. In other tissues the organism grows as a coarse mycelium.[8]

This organism has been a very uncommon pathogen in man. It is known to produce paronychias in orange pickers, and occasional cases of otomycosis. It not infrequently is a secondary invader in chronic pulmonary infection and occasionally is the primary cause of pulmonary disease.

Five of the previously reported cases of mucormycosis of the central nervous system were in diabetic adults.[2, 3, 4] In all of these cases the eye was involved, and the portal of entry for the organism was thought to be the eye or the paranasal sinuses. In the sixth case, reported by Paltauf[1]

in 1885, the primary infection was in the lungs, but metastatic abscesses developed in the central nervous system and other organs before death.

The case presented here is the first mucor infection of the central nervous system reported in an infant. It bears a striking resemblance to those reported by Gregory and associates[2] but no evidence of diabetes was found.

In recent years, interest in mycotic infections has been steadily increasing. In 250,000 admissions to the Duke University Hospital, Smith[9] reported 207 cases of mycosis. None of these were mucor. Infection of the central nervous system by fungi occurred in ten cases among 17,400 autopsies at the Johns Hopkins Hospital.[10] At the Mayo Clinic, five of 104 metastatic brain abscesses were due to mycotic organisms.[11]

Although the incidence of generalized severe mycotic infection is still low, the question, "Are fungus infections increasing as a result of antibiotic therapy?" has been raised. This question has been well answered by Kligman[12] who believes that if the bodily defenses of a patient are lowered by serious illness, malnutrition, surgical trauma, or old age, antibiotic therapy may destroy the normal bacterial flora of the body and allow "opportunistic fungi," which ordinarily have a low degree of virulence, to produce fatal infections. In this way, antibiotics may have been an indirect cause of mycotic infection in this infant with severe diarrhea and dehydration.

The etiology of arterial thrombosis in infancy is obscure. Gross[5] thoroughly reviewed the literature and lists sepsis, congenital heart lesions, trauma, faulty closure of the ductus arteriosus, and thrombosis of a nonfunctioning umbilical artery extending outward. He felt that infection was a rare cause of thrombosis of a large vessel. Other authors reported similar etiologies.[13, 14, 15, 16, 17, 18] In addition, they suggest constricting amniotic bands, angiospasm,[19] and "intimal agglutination" due to injury of arteries following difficult deliveries.[20]

In the case presented, the thrombosis was apparently due to infection. The known affinity of the mucor organism for blood vessels makes it a logical offender. Increased viscosity of the blood resulting from dehydration may have been a contributing factor in the production of this thrombosis.

The diagnostic findings in arterial thrombosis are due to absent blood supply in the affected area. Diagnosis of arterial thrombosis in an extremity is relatively easy while "damage to the brain by arterial occlusion may produce a clinical picture which is easily recognizable or extremely confusing."[5] The condition may be associated with convulsions and loss of consciousness. The onset may be sudden or insidious and the neurological findings may be focal or bizarre and nonlocalizing. An interesting finding in the case presented was the marked increase in all the spinal fluid findings. In retrospect this is thought to be due to actual necrosis of brain tissue.

Treatment of the conditions discussed is chiefly supportive. When an effective therapeutic agent is available, infection should be vigorously treated. Potassium iodide may be of some use in the treatment of infection with mucormycosis.

SUMMARY

The first reported case of mucormycosis of the central nervous system in infancy has been presented. The mucor organism is believed to have produced the third recorded case of infantile carotid artery thrombosis. The unusual ability of this fungus to invade blood vessels and to occlude their lumina has been pointed out. The role of antibiotic therapy in mycotic infection is discussed. No effective therapy is known for this condition.

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POISONING FROM NAPHAZOLINE (PRIVINE) HYDROCHLORIDE

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URBANA, ILL.

NAPHAZOLINE (Privine) hydrochloride is a potent local vasoconstrictor used especially in the nose. Frequent use as nose drops commonly results in "rebound" congestion of the mucosa, although renewed application continues to produce brief constriction.[1] It is recognized that indiscriminate use of any nose drop is an unwise procedure and that many patients use such preparations too frequently without knowledge of their limitations and contraindications.[2, 3, 4, 5] Fortunately, toxic reactions are usually confined to mild local or rare systemic effects.

Waring[6] reported three children in whom intranasal or ingested naphazoline hydrochloride produced sedation. In each instance, mild drowsiness was the only symptom. The author reported that intravenous doses in rats and dogs produced hyperpnea, gross muscle spasms, occasional reflex hyperexcitability, and convulsions. The effects of fatal doses suggestively resembled acute epinephrine deaths.

Two reported children treated with intranasal naphazoline hydrochloride developed pallor, shallow respirations, and mild lethargy.[7] Hainsworth[8] reported a more severe reaction in a 22-month-old child following accidental ingestion of an estimated 3.0 to 4.0 c.c. of the 0.1 per cent solution. Irritability, bradycardia, lethargy, pallor, gasping respirations, dilated pupils, hypertension, and cold clammy skin were the findings in his patient. In all reported cases of poisoning or hypersensitivity from naphazoline hydrochloride, recovery has been complete, usually within six or eight hours.

Because of the relative rarity of reports of severe intoxication from Privine, we are reporting two small children with alarming reactions from ingestion or intranasal instillation of the preparation. The dangerous potentialities of this preparation in childhood are evidenced by the clinical picture in each instance.

CASE REPORTS

CASE 1.—D. D., female, aged 3½ years, was seen on Sept. 28, 1953. She had had instilled at 2:30 P.M. into her nostrils an unknown quantity (estimated less than 5.0 c.c. by the mother) of 0.05 per cent Privine hydrochloride solution. One-half hour subsequently she had become pale and limp and the skin had become cold and clammy. She was brought immediately to the hospital and was examined within one hour after the nasal instillation.

Examination disclosed a conscious, pale, highly irritable child with cold, clammy skin. At intervals she cried out with "pains in the head." Respirations were slowed. Rectal temperature was 99.4° F., pulse 60 beats per minute, and blood pressure unobtainable. The pupils were of moderate size and reacted to light. Explosive vomiting occurred once. She appeared seriously ill and in collapse.

She was hospitalized and observed, but no specific therapy was given

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other than to provide added warmth. During the early evening hours she was restless, the skin was cool and moist, and the bradycardia persistent. In the late evening she fell asleep without sedation and slept all night. On the following morning she was alert and cooperative, and the skin was pink and warm. The temperature was 99.0° F., pulse 120 beats per minute, and blood pressure 85/54. A complete physical examination at this time was noninforming. Urinalysis was negative, and an electrocardiogram was within normal limits. A complete blood count was in the normal range except for a leukocyte count of 17,600. Recovery was apparently complete.

CASE 2.—D. P., male, aged 2½ years, the son of a physician, was not observed; the history and observations were reported in a personal communication by the physician-father. The child had ingested an unknown quantity of 0.05 per cent Privine hydrochloride solution. Within thirty minutes he had appeared drowsy and had been unresponsive. Pallor, cold moist skin, and drowsiness had been prominent. He had been taken immediately to a hospital and on arrival had been unconscious, flaccid and pulseless, and apparently had expired. An intravenous infusion of 5.0 per cent dextrose in water had been started. Within minutes after initiation of the infusion his condition had improved, and within four to six hours he had appeared normal in all respects. During the acute phase his condition had been so critical that there had been no time for physical examination or pulse, blood pressure, and temperature determinations.

COMMENT

Naphazoline (Privine) hydrochloride is one of a series of imidazoline derivatives, the chemical name being 2-(l-naphthyl-methyl)-2-imidazoline hydrochloride. It is primarily a vasoconstrictor possessing the chief pharmacological properties of epinephrine on peripheral vessels. The commercial preparation is an isotonic, buffered, aqueous solution, adjusted at a pH of 6.2 to 6.3 and available in 0.05 and 0.1 per cent concentrations. The first concentration is recommended for use by the patient, the second strength being reserved for direct use by the physician.

The incidence of systemic reactions to Privine hydrochloride in childhood apparently is not frequent. However, the possibility of severe reactions is to be considered when the medication is used to treat patients of the younger age groups. The principal systemic manifestations of poisoning are bradycardia, bradypnea, lethargy, hypertension, cold clammy skin, and normal or subnormal temperature. Despite the severe clinical picture of poisoning in childhood, recovery has been complete after several hours in all documented cases.

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TRACHEOTOMY IN AN ELEVEN-WEEK-OLD INFANT WITH BULBOSPINAL POLIOMYELITIS

Case Report and Brief Summary of the Literature

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CASES of poliomyelitis in infants under 6 months of age are relatively few. In 1918, Gunewardene[1] recorded the history of an infant 12 days old who had extensive spinal poliomyelitis and recovered. Biermann and Piszczek,[2] in 1944, reported a case of poliomyelitis on the eleventh day of life, with fatal termination on the sixty-seventh day. The infant had been exposed for ten minutes to his mother, who showed signs of poliomyelitis on the first post-partum day, and who died three days thereafter. In 1948, Harm and Weidenthal[3] described a case of polioencephalitis in a 3-week-old infant. In a review of the literature since 1870, Mouton and associates[4] could find only seventeen cases in infants under 6 months. They went on to record ten more cases of their own which occurred in the county of Los Angeles in 1948. During the 1950 epidemic in Northern Ireland, McConnell reported the disease in ten infants under 6 months of age, out of a total of 243 cases admitted to the Northern Ireland Fever Hospital. One of the youngest patients in the literature was that of a 5-day-old infant with polioencephalitis. This was reported by Baskin, and co-workers.[7] In 1950 five cases among infants during the neonatal period were reported from New York City by Abramson and associates.[5] The youngest in their group was 4 days old.

Address: Children's Hospital.

It is generally accepted that until the sixth month of age, infants possess a passive immunity to poliomyelitis. The foundation for this belief was the work of Aycock and Kramer[10] in 1930. They showed that serum from the cord blood of ten out of twelve newborn infants possessed the same neutralization power to poliomyelitis virus as did the blood serum of their mothers. While the incidence of poliomyelitis in pregnant women is increased,[9] in no instance has the fetus shown evidence of the disease at birth. The appearance of poliomyelitis before the fifth day of life would indicate infection in utero. Though the virus is usually limited to the gastrointestinal tract and the central nervous system, it has been isolated from the blood.[8] This fact indicates that the fetus of a mother ill with poliomyelitis could be infected via the placenta in the course of a maternal viremia.

During the 1952 epidemic of infantile paralysis in Manitoba, over 250 children under the age of 15 years were admitted to the Children's Hospital of Winnipeg. There were fifteen cases in children under the age of 12 months. Seven patients with this disease were under 6 months of age.

The following report concerns an infant 11 weeks of age, with bulbospinal poliomyelitis, who had a tracheotomy performed and who was confined to a Drinker-Collins respirator.

CASE REPORT

Baby A. C., aged 11 weeks, was admitted Oct. 29, 1952. This male infant was born on Aug. 10, 1952, of a normal nine-month pregnancy. His course was quite satisfactory until October 20, when it was noted he had a slightly elevated temperature. The mother also observed that when he cried he made no sound. He appeared listless during the following five days, and the mother observed that the child reacted sluggishly to his external environment. A few days previously he had been in contact with a 3- and 4-year-old brother and sister both of whom developed poliomyelitis. On October 27 she noted a definite drooping of his upper eyelids.

On October 28 he was admitted to another hospital with a temperature of 98.2° F. The respiratory rate was 30 per minute, and the pulse was 110. Lumbar puncture revealed a clear fluid under normal pressure and with a total of 60 cells per cubic millimeter (49 lymphocytes, 11 polymorphonuclears).

At 1:30 A.M. of the next day (fourteen hours after admission) it was noted that the respiratory rate was 60 per minute and was shallow and very irregular. Thirty minutes later the infant was transferred to Children's Hospital.

There was no cyanosis on admission, but the child's range of respiration was shallow and the rate was 70 per minute. The infant had an overly alert and anxious countenance. He was experiencing severe difficulty on inspiration. The respiratory movements were restricted to the diaphragm and sternomastoid muscles. Almost all of the breathing was done by the accessory muscles of respiration. There was no pooling of secretions, and the only overt clinical neurological findings were a left facial paralysis, as well as some weakness of the hip abductors, the inward and outward rotators, and quadriceps on the left side. There was no other muscular involvement.

Thirty minutes later the child's rectal temperature was 99° F., pulse 152; the respiratory rate was 52 and grossly irregular. The respirations became progressively more labored, and the child began to develop difficulty in handling pharyngeal and oral secretions.

It had become apparent that due to his inability to swallow, oropharyngeal obstruction had developed. There was marked pooling of secretions in the upper respiratory tract. Because of the rapid deterioration, the child was placed into a tank respirator. Almost immediately it was observed that this measure decreased his respiratory distress, and it was decided that a tracheotomy would have to be done before the respirator could be used with safety and benefit by the infant. The indications for tracheotomy here were: (1) to assist in maintaining a clear unobstructed airway, and (2) to prevent aspiration of secretions deep into the lung by the action of the respirator.

The immediate postoperative result in this child was most dramatic. His color improved almost at once. His respirations became less difficult and secretions were easily suctioned via the tracheotomy tube. Shortly after the procedure, the infant fell into a restful sleep. He was placed into a Drinker-Collins respirator maintained at a negative pressure of 20 mm. of water, and a respiratory rate of 28 per minute.

Nothing was given orally, but Estopen 300,000 I.U. daily, plus 75 c.c. of 10 per cent Travert followed by 150 c.c. of 5 per cent Travert mixed with 75 c.c. of Darrow's solution were given intravenously. The child was maintained on intravenous therapy via scalp vein for the next eight postoperative days. He was given fluids equal to 50 c.c. per pound of body weight per day, consisting of 10 per cent and 5 per cent Travert in water, plus Darrow's solution, vitamin K, and intravenous multivitamins. Estopen and intravenous Aureomycin were also administered postoperatively. Continuous oxy-

gen and steam were given via the tracheotomy tube.

The child's course during the first postoperative days was uneventful. Within twenty-four hours after the tracheotomy it was possible to remove the infant from the respirator for a twenty-minute interval without causing any respiratory distress. After about eighteen hours the child began to coordinate with the respirator. Except for two brief blue spells while out of the machine on the third and fourth postoperative days, his course was uneventful. It became possible to remove the child from the tank for periods up to one hour.

By the eleventh postoperative day he had progressed so well that he could stay out of the respirator for periods up to ninety minutes. There were minimal signs of skeletal involvement; the child was alert and showed no cerebral involvement.

By the seventeenth postoperative day the child was swallowing well, and tolerated his feedings. His color was good while out of the respirator, and the tracheotomy tube was removed.

On the twenty-seventh postoperative day the child was discharged from the hospital with no evident sequelae.

The infant was seen again at 22 weeks of age. The tracheotomy wound had healed satisfactorily, and the only clinical evidence of the child having had poliomyelitis were his weak hip abductors and inward rotators.

DISCUSSION

Although poliomyelitis is not common during infancy and must be rare during the first month of life, several known cases have been reported. A review of the literature revealed no previous patient in whom tracheotomy had been performed successfully, for this disease, so early in life. This case demonstrates that the indications for tracheotomy in bulbospinal poliomyelitis are no different in an infant than they are in an adult. Certainly age is no contraindication to tracheotomy.

SUMMARY

1. A brief report of the recorded cases of poliomyelitis in infancy has been presented.

2. The case of an 11-week-old infant with bulbospinal poliomyelitis, who required both a tracheotomy and a mechanical respirator, has been discussed.

3. This case also demonstrated that patients who could not handle their oropharyngeal secretions, or could not swallow, should not be placed into a mechanical respirator before tracheotomy was performed.

The tracheotomy in this case was performed by Dr. Richard Burrell.

I wish to thank Dr. J. Graf for permission to publish the case.

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Medical Progress

RADIOTHERAPY IN TUMORS OF CHILDHOOD

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IONIZING radiation for the treatment as well as the diagnosis of disease began shortly after Roentgen's historic discovery in 1895. In chronological comparison with medicine and surgery, radiotherapy has been in general use only a relatively short time, yet it has achieved a position of comparable therapeutic importance to the curative measures relied on by physicians for many centuries.

The purpose of this paper is to present our impressions of the value and limitations of radiotherapy in juvenile neoplastic disease. It is not intended to be a critical evaluation of all radiotherapeutic results reported on children.

Several facts must be recalled:

1. The minimal amount of ionizing radiation which will not cause cellular damage has not been determined. Therefore damage, in the broadest sense, may be expected to occur whatever the dose is.

It is well known that other bodily "insults" such as trauma, heat, cold, chemicals, and infections may also be expected to cause cellular damage—sometimes mild and at other times severe enough to produce necrosis. The amount of cellular recovery is usually dependent not only on the quality and degree of the "insult" but also on the reparative potential of the "injured" body. The remarkable capacity of children to recover from even extreme forms of "injury" is common knowledge. Significant clinical recovery from moderate or slight irradiation injury also occurs in children. How complete and how permanent is such recovery can only be inferred by the meager observations made up to the present.

2. The high case mortality of children's cancers, the delay in diagnosis and therapy not only have precluded an objective estimate of the value of radiation as a therapeutic agent in these conditions, but from the biological standpoint, these factors have permitted a long-term follow-up appraisal (fifteen or more years) of the associated effects of radiation on skin, blood vessels, bone, viscera, etc., in only a limited number of cases.

Other questions arise in the attempt to establish unvarying standards for procedure:

a. To what degree can experimental animal evidence be utilized in interpreting "analogous" dosage in the child?

b. Can results observed in the mature human being be used for comparative purposes in such a physiologically (as well as structurally) different individual as a child?

Following irradiaition, significant, at times severe, alterations occur very rapidly in somatic as well as germ cells, and it has been repeatedly demonstrated experimentally that per-

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manent mutations occur. Clinical reports of serious postradiation sequelae in children are, however, very sparse.

In a survey of thirty-four children who had received irradiation in which the spine was included in the field of therapy Neuhauser[1] concluded that "dosage in excess of 2,000 tissue r, irrespective of the age of the child, will probably produce growth disturbances." Deleterious sequelae in the skin,[2] bones,[3] and kidney have been described and considered to be the results of faulty technique or overdosage.

The use of radium applicators for the treatment of hyperplastic lymphoid tissue in the nasopharynx has broadened greatly. In the words of Crowe and Loch[4] ". . . so far as we know there has never been a radium burn or a new growth arising in the irradiated area among the thousands of cases we have treated during the past 25 years." Schneider,[5] however, states, "The radium applicator produces excessively high dosage at its surface and a rapid fall off within a few mm. The possibility is serious that late sequelae such as atrophic rhinitis or worse may occur."

BIOLOGIC AND PATHOLOGIC OBSERVATIONS

The roentgen rays and gamma rays in common therapeutic use occupy only a small part of the electromagnetic spectrum, having wave lengths between 10^{-8} and 10^{-10} cm. Absorption of this radiant energy in matter occurs by a process called ionization, in which the radiation photons* or quanta* behave like particles and eject orbital electrons from atoms by elastic collisions; the ejected electrons ionize further atoms until brought to rest (Fig. 1). The roentgen—symbol r—is a physical unit of quantity of radiation based on the amount of ionization produced by its absorption in air. Therapeutic doses of radiation are recorded in roentgens, just as doses of drugs are recorded in grams, but in neither case is the therapeutic effect necessarily proportional to the dose, nor does a given dose always produce the same effect.

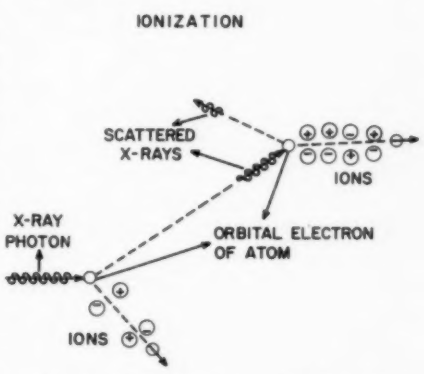

Fig. 1.—Ionization, schematic diagram.

The biologic effect of ionizing radiation is primarily an injury to the cell. The forms of the injury are very diverse, such as changes in permeability, inhibition of enzyme reactions, alterations of function, breakage of chromosomes, and inhibition of mitosis, but in general (if they are not immediately lethal) they all shorten the life of the cell, even though recovery from the

*Newton regarded radiations as having a corpuscular nature, but Huyghens showed that radiations have a wave motion. In their interaction with matter, electromagnetic rays behave like corpuscles or particles. The term photon denotes such an ultimate particle of radiation, in the same way as the term atom denotes an ultimate particle of a material element.

*Radiant energy is not absorbed nor emitted continuously, but in discrete amounts called quanta. A quantum is an elemental unit of radiant energy. The energy of a quantum depends upon the wave length of the radiation; for example, for 100 kv. x-rays it is approximately 4×10^{-8} erg. sec., and for 1,000 kv. x-rays, 5.5×10^{-8} erg. sec. The term quantum is thus almost, but not quite, synonymous with the term photon.

injury may appear to be complete. The clinical effects of therapeutic irradiation are the end result of all these injuries modified by the reparative and homeostatic reactions of the body.

Radiosensitivity.— Radiosensitivity and its converse, radioresistance, are terms used to explain the observation that different cells, tissues, organs, or organisms differ in their response to a given radiation dose. In radiobiology the LD_{50} is a convenient measure for comparing radiosensitivity; for example, under certain standard conditions of exposure, age, weight, strain, etc., guinea pigs with an LD_{50}* of 200 r are more radiosensitive than mice with an LD_{50} of 450 r. In clinical radiotherapy comparable measurements of the radiosensitivity of, for example, normal and malignant cells have not been made, but a variety of inferential observations has been built up into a concept of radiosensitivity which is now more a hindrance than a help in the treatment of patients with cancer.†

This concept stems from a very early explanation of the nature of radiosensitivity in the "law" of Bergonie and Tribondeau[6] that "the sensitivity of cells to irradiation is in direct proportion to the reproductive activity of the cells and in inverse proportion to their degree of differentiation." As a general statement it is true that cells in the process of mitosis are more radiosensitive than in the resting state, and that embryonic tissues, at any rate at certain stages of development, are more radiosensitive than their adult counterparts. The extension of this concept to cancer supposes that the cancer cells are more radiosensitive than the analogous normal cells because they are less differentiated and have greater mitotic activity, proceeds to further assumptions that increasing "de-differentiation" or anaplasia of the cancer, and increasing malignancy,* imply greater radiosensitivity, and ends in absurdities such as that well-differentiated, slowly growing cancers are radioresistant and should therefore be treated surgically, or that highly malignant cancers ought to be more easily curable by irradiation than those of lower malignancy.

A few observations must suffice to illustrate the inadequacy of this prevalent concept of radiosensitivity in clinical radiotherapy: medulloblastoma, neuroblastoma, Ewing's tumor of bone are very radiosensitive but seldom cured; basal-cell carcinoma of the skin, about the least malignant of cancers, is both radiosensitive and radiocurable; a benign tumor, the cavernous hemangioma, is more radiosensitive than any malignant tumor. Even among normal cells, the spermatozoa are more radiosensitive than their parent spermatogonia, polymorphonuclear leukocytes than the stem cells in the bone marrow, and lymphocytes than their precursors in the lymph-germinal centers.

Another aspect of radiosensitivity often encountered is the classification of the normal cells of the body in order of sensitivity, and then analogous classification of malignant tumors.

*The LD_{50} is the average dose which causes a 50 per cent mortality.

†We use the term cancer in its oldest sense, meaning a malignant growth of tissue. It is thus an inclusive term; carcinoma, sarcoma, embryoma, etc., denote subdivisions of the general term.

**Degree of malignancy* is a clinical term used to indicate the rate of progress of cancer, such as slow or rapid growth, early or late dissemination. It thus carries some implication as to prognosis. It is also used in pathologic reports in a somewhat different sense, as a kind of shorthand notation to give the pathologist's opinion of the degree of malignancy.

An oft-quoted list of normal cells[7] begins with lymphocytes and leukocytes, then epithelial cells, endothelial cells, connective tissue, muscle, bone, and ends with nerve cells as the least radiosensitive. But the attempt to make the different types of cancer fit into an order of radiosensitivity corresponding to that of the analogous normal cells soon breaks down; lymphosarcoma and neuroblastoma, which would come at opposite ends of such a list, are in fact both very radiosensitive—and many similar discrepancies could be given.

Indirect Radiation Effects.—The degree of radiosensitivity appears to be an inherent property of each type of cell, with variations in different stages of its life cycle, but it is also modified by extrinsic factors. Local factors such as anoxia, edema, infection, scarring, and previous irradiation decrease radiosensitivity, so that the condition of the "tumor bed"* assumes as much importance in clinical radiotherapy as the inherent radiosensitivity of the cancer cells. The indirect effects of irradiation appear as an inflammatory reaction of the tissues of the tumor bed, such as changes in the endothelium of blood vessels and lymphatics, phagocytosis of dead and damaged cells, and replacement fibrosis. Holfelder[8] emphasized the importance of these indirect radiation effects in the successful treatment of cancer in the aphorism "There is no cure of cancer by irradiation without fibrosis," and Graham[9] thought they were a more reliable index for prognosis than the direct effects on the cancer cells.

*We use this term to denote all those normal cells and tissues either within a tumor or immediately adjacent to invasive malignant cells at the periphery of the tumor. It is *not* used to mean the tissues lining the cavity left after the surgical extirpation of a tumor.

There are also general factors which alter radiosensitivity; for example, it is increased in thyrotoxicosis and diabetes mellitus, and decreased in anemia, malnutrition, and malignant cachexia. Current investigations combining radiotherapy with chemotherapy and with hormones may reveal other general factors which alter radiosensitivity, and investigations are also proceeding with "protective" and "sensitizing" agents such as systeine and oxygen, respectively.

Cancerocidal Dose.—The clinical cure of a malignant tumor by irradiation involves a combination of the direct effects on the cancer cells, the indirect effects of an inflammatory reaction in the tumor bed, and probably some degree of response in the patient as a whole. Thus in the strict sense a cancerocidal dose can only be defined in vitro, but it is loosely used to mean the average in vivo tumor dose required for clinical cure. The best available assessment of clinical cure is the five-year disease-free survival rate, but adequate statistics of this sort have been compiled for only a few types of cancer; for many types of cancer either the survival rate is too low or the number of cases with localized disease consistently treated (particularly in children) too few. Thus the clinical cancerocidal dose (sometimes called the tumor lethal dose) is known with some precision only for epidermoid carcinoma (5,000 to 7,000 r) and for malignant lymphoma (2,000 to 4,000 r.)

The Time Factor.—Every biologic effect of irradiation is the end result of two opposing processes, the radiation injury and the reparative response. There is always a latent in-

terval between the irradiation and the appearance of the injury, and the recovery period is also a function of time; hence the dose of radiation and the time occupied for its delivery are inseparable factors in the production of radiation effects. If the radiation injury occurs at a slower rate than the rate of recovery, no effect will be demonstrable; this is the basis of the tolerance dose of 0.3 r per week prescribed for personnel exposed to radiation. Since different cells and tissue have both differing rates and differing powers of recovery, the time factor can be exploited to obtain differential effects. Thus for some types of cancer there is a dose-time combination from which the malignant cells cannot recover but which permits the recovery of the normal tissues; these are the "radiocurable" cancers such as epidermoid carcinoma, some adenocarcinomas, seminoma, lymphosarcoma, etc. For other types of cancer no dose-time relationship has yet been found which will consistently sterilize the tumor without also producing radionecrosis of normal tissues; this "radioincurable" group includes osteogenic sarcoma, malignant melanoma, glioblastoma, etc.

Although dose fractionation has been for thirty years the most commonly used technique in radiotherapy, no general principles have been established which would indicate the optimum dose-time combination either for a particular type of cancer or for its situation in the body. The technique which succeeds in curing carcinoma of the lip fails in carcinoma of the pharynx, or the technique which will cure a bone metastasis from carcinoma of the breast is ineffective in treating the primary tumor, and so on. Radiotherapy is still more an empirical art than an exact science.

The Volume Factor.—The effects of a given dose of radiation increase as the volume of tissue to which it is administered increases; for example, a dose of, say, 400 r to the thigh produces nothing more than a transient erythema of the skin, but given to the whole body is lethal. It is not only that a large tumor usually has a worse prognosis than a small one, but also that the radiation dose which can *safely* be given to the large tumor is always less, and often much less, than can be given to the small one.

Homogeneous Dosage.—The concept of a tumor lethal dose logically entails that every part of the tumor be given this dose, just as the concept of surgical cure entails the removal of every malignant cell. The reasonableness and the practical value of homogeneous dosage throughout the estimated volume of cancer-invaded tissues are not in doubt, but it is not sufficiently realized that the homogeneity is only on the macroscopic scale. On the cellular scale, and still more on the molecular scale, uniform ionization is impossible.

Since cancers are cured by irradiation even though at the cellular level the dose is not homogeneous, nonhomogeneous dosage on the macroscopic scale has been intentionally practiced in recent years through the use of "grid" therapy for two reasons: first, repair of the normal tissues can be preserved, since if radionecrosis occurs in the zones of high dosage (under the holes in the grid), it can be repaired from adjacent, relatively undamaged tissues in the zones of low dosage (under the lead

parts of the grid), and, second, large tumors which are incurable by homogeneous dosage (because the dose which can safely be given is not curative) can perhaps to broken up into small cylinders and sterilized piecemeal.

The Age Factor.—In pediatric radiotherapy it is usually assumed that doage should be related to age, in much the same way as pharmacological dosage; the latter, however, is in fact related to weight rather than to age, and so is not applicable to radiation dosage. There is abundant evidence in embryology that with each developing organ there is a critical period when it is highly sensitive both to irradiation and to a variety of other noxious agents. In the infant and child, however, there is apparently no difference in the reactions of most tissues and organs to a given dose of radiation from those in the adult. For example, the production of a skin erythema or an epithelitis of a mucous membrane requires the same dose-time combination in children as in adults, and certainly the cure of childhood cancers is not obtained by any smaller dose than is required for the corresponding tumor in adults. It would seem that if children's tissues are more radiosensitive than adults', the increased radiation damage is probably counterbalanced by a greater power of recovery. There is, however, one important exception in areas of bone growth; epiphyseal cartilage and centers of ossification are very easily damaged by irradiation. While recovery usually occurs, the period of interruption of growth leaves a permanent effect in shortening of a long bone or malformation of other bones.

The Wave-Length Factor. — Although monochromatic radiation is not available for clinical use, the "filtered" beams from x-ray tubes and radioactive sources are sufficiently homogeneous to be given an average wave length. The penetration (depth dose), the spatial distribution of ionization, and the atomic absorption coefficients are the main variants with wave length which have clinical implications.

An important principle in radiotherapy concerns the protection of normal tissues and aims at delivering the required tumor dose with the least possible dose to surrounding and overlying structures. A proper choice of wave length—longer wave lengths for superficial lesions, shorter wave lengths for deeper ones—is one means for achieving this aim, although others, such as the geometrical arrangement of tangenital and cross-firing beams and the optimum focus skin distance, are of equal importance.

The spatial distribution of ionization tends to become more uniform with shorter wave lengths, which in theory should mean more effective irradiation at the cellular level, but its clinical importance is uncertain and awaits statistical proof that the results of supervoltage x-ray therapy, for example, are better than those obtainable at lower voltages.

The energy absorbed per roentgen varies with the wave length of the radiation according to the atomic number of the elements concerned. For example, with 140 kv. x-rays bone absorbs several times more energy than soft tissue, but with 1,000 kv. x-rays only 10 per cent more; hence when normal bone is in the irradiated

field it is preferable to use radiation of shorter wave length.

Skin reactions are also less intense with hard radiation than with soft, as the zone of maximum ionization is shifted deeper into the body with increasing voltage.

Radiation Damage to Normal Tissues.—It has already been mentioned that the successful radiotherapy of cancer either requires, or at any rate entails, an aseptic inflammatory reaction in the normal tissues. Although recovery from these early radiation reactions usually appears to be complete, further changes may occur after an interval of months or years which indicate that some permanent damage was in fact produced. These changes are readily observed in the skin and accessible mucous membranes as telangiectases, dryness, atrophy, fibrosis, etc., but it should be realized that similar late effects may occur in any tissue which has received the level of radiation dose necessary in the treatment of cancer, for example, pulmonary fibrosis, radiation fractures of bone, cataract, and even radiation sarcoma. These late changes suggest that every irradiated tissue may have lost some of its natural resistance and be unduly susceptible to quite minor degrees of trauma or infection; indeed, since severe late radiation injuries occur in only a small proportion of cases, it seems possible that trauma, infection, sun bathing, etc., may be contributing factors. Radiologists should try to prevent late reactions by simple instructions to the patient, careful supervision at follow-up visits, and detailed explanation to the family doctor.

The term "genetic injury" is usually restricted to radiation-induced mutations in the sex cells which might result in the production of abnormal offspring. Genetic injuries, of course, also occur in somatic cells and their consequences may well be of greater importance than those in germ cells; hence it is a cardinal principle in radiotherapy—which might perhaps be extended to diagnostic radiology—not to irradiate any tissue, somatic or germinal, unnecessarily.

The Nature of Cancer.—It is not difficult to deduce from the above summary of the bases of radiotherapy that our knowledge is pitifully inadequate for the scientific treatment of cancer in children. It would seem appropriate, therefore, to end this section with some remarks on the nature of cancer and its course in children, since these ideas so largely influence our approach to treatment.

The concept that cancer is a completely autonomous, steadily progressive growth with an irreversible course is no longer tenable even in adults. Carcinoma in situ may exist for many years before it becomes invasive, and sometimes perhaps it disappears without ever becoming invasive cancer. The progress of some cancers of the breast and prostate is halted or reversed by hormone therapy, which suggests that some of the five-year "cures" ascribed to surgical removal or radiotherapy may in part be mediated through naturally occurring hormonal changes. The spread of the age incidence of typical childhood cancers such as acute leukemia, medulloblastoma or Wilms's tumors into adolescence and adult life, or the appearance of malignant change in teratomas and other initially benign tumors, likewise suggest that the host retains for a longer or

shorter time some humoral control over their invasiveness.

In the first few years of life the neoplastic process might be initiated by alterations of the humoral factors which normally control growth and development. Thus it is our aim in treatment to control the cancer for as long as possible so that the child may have a chance of developing its natural means of "cure," if such exist, and so to record our observations on the effects of treatment that the nature of these humoral factors may possibly be discovered.

The practitioner's decision on the use of radiotherapy must be based on several considerations:

1. Does the case require radiotherapy?
2. If so should it be used
a. as the sole therapeutic agent,
b. as a combined method with surgery pre- or postoperatively,
c. as a palliative measure?

The age and condition of the patient, the site as well as the histologic identity of the tumor, the presence (if any) and degree of metastases are factors which must also guide his judgment.

As in any other form of therapy it must be clearly recognized that just because a disease responds to a given method it does not follow that other methods might not be equally or perhaps even more effective. For example, hemangiomas respond well to ionizing radiation. This does not mean that all hemangiomas should be so treated for actually very few hemangiomas require any of the various types of recommended treatment at all. Neuroblastomas will usually respond to radiotherapy. However, if removal of the primary neuroblastoma is surgically feasible such a procedure should be undertaken.

INDICATIONS FOR RADIOTHERAPY IN CHILDREN'S TUMORS

These may be briefly considered under the headings positive, questionable, and negative.

1. *Positive:*

a. Radiosensitive cancers which may or may not require surgery as a preliminary or supplementary procedure.

b. Any malignant tumor in which surgery is deemed impracticable *whether or not it appears radiosensitive by histologic examination.*

2. *Questionable:*

a. Certain benign tumors (hemangioma, lymphangioma) and granulomas (nonlipid reticuloendotheliosis). Many considerations are to be thought of in such cases—does the case require *any therapy,* have more conservative measures been rejected, the age of the patient, the site (or sites) and rate of growth of the tumor(s).

b. Certain palliative measures (intractable bone pain in leukemia, tracheal obstruction from extreme pressure by lymphosarcoma).

3. *Negative:*

Pigmented nevi, melanoma, most benign tumors.

In children the following tumors have responded in varying degrees to ionizing radiation:

Skin and "Soft Somatic" Tissues

Benign	*Malignant*
Hemangioma	Sarcomas of several types
Capillary	Fibrosarcoma
Cavernous	Myxosarcoma
Lymphangioma	Rhabdomysarcoma
Cystic hygroma	Liposarcoma
Infections granulomas	Granulation-cell sarcoma
Keloid	Neuroblastoma

Papillomatosis of larynx
Nasopharyngeal Polyposis
Fibroma

Central Nervous System

Intracranial	*Spinal*
Medulloblastoma	Intramendullary—same as in the brain
Astroblastoma	Extramedullary hemangioblastoma
Ependymoma	Ganglioneuroblastoma
Glioblastoma multiforme	

Intracranial—Cont'd
Pinealoma
Meningeoma
Hemangioblastoma
Craniopharyngioma
Pituitary adenoma
Glioma of optic chiasma

Thoracic

Primary	*Metastatic*
Lymphosarcoma	Metastases from:
Malignant thymoma	Wilms's tumors
Neuroblastoma	Rhabdomyosarcoma and other soft tissue sarcomas
Teratoma	Teratoids
	Neuroblastoma, retinoblastoma
	Osteogenic sarcoma
	Ewing's tumors
	Embryonal carcinomas

Abdominal, Pelvic, Retroperitoneal and Genital Sites

Wilms's tumors
Hepatic—mesenchymoma
Neuroblastoma
Sarcomas
Teratomas
Adenocarcinomas
Seminomas
Dysgerminoma

Lymphoid and Hematopoietic Tissues

Myelocytic leukemia
Hodgkin's disease
Lymphosarcoma
Leukemia infiltrations—pharynx, meninges, kidneys, etc., in acute leukemia

Bone

Fibrosarcoma
Osteogenic sarcoma
Ewing's tumors
Reticulum-cell sarcoma
Giant-cell Tumors
Hemangioma—usually of vertebra

Miscellaneous

Reticuloendothelioses (nonlipoid)
Thyroid carcinoma
Retinoblastoma

APPARATUS AND METHODS

Selective Absorption of Radioactive Isotopes.—The use of a radioactive substance that was absorbed only by cancer cells would be the ideal method for delivery of the requisite tumor dose with the least exposure of normal tissues. Only the absorption of radioiodine by functioning thyroid tumors meets this requirement at present.

Interstitial Irradiation.—The insertion of radioactive sources in and around a malignant tumor is an efficient means of administering a high tumor dose with minimum exposure of normal tissues, but has few present applications in children; in the past, radon seeds have been used in the treatment of retinoblastoma and hemangioma.

External Irradiation.—External irradiation has a wide range of flexibility, so that by a suitable choice of kilovoltage, filtration, focus skin distance, field size, and beam geometry, the requisite tumor dose can usually be delivered without exceeding normal tissue tolerance. Radium as an external source of radiation has been almost entirely superseded by x-ray apparatus operating at voltages from 50 to 1,000 kv., but radioactive cobalt is an economical alternative for a 2,000 kv. x-ray machine.

In the megavoltage range several betatrons operating at 22 million volts are now in use. As x-ray sources their advantage is that the entrance dose is only one-third and the exit dose about two-thirds of the maximum dose in the tumor; if used as beta-ray sources (electron-beam therapy), the entrance dose and tumor dose are approximately equal, but the exit dose is virtually zero.

Methods of Irradiation.—Intensive fractionated x-ray therapy is the method most often used in the treatment of cancer in children, and generally means daily doses of equal size for a period of one to five weeks. Although there are innumerable variations in the time intervals between

successive doses, the amount of each dose, the dosage rate, and the over-all time of treatment, none has obtained such outstanding results as to win universal acceptance. In many cases the plan of treatment is modified to a greater or lesser extent according to the radiotherapist's day-to-day observations of the effects on the patient and on the tumor, so that the present practice of radiotherapy is much more individualistic than that of surgery.

The Radiotherapy Consultation.—Although the diagnosis may have been established before the radiotherapist is consulted, he needs his own physical examination of the patient and review of the history and laboratory data in order to judge the possibilities of treatment, and particularly whether there is a reasonable chance of cure or whether treatment is likely to be only palliative.

A general plan of management having been agreed upon and the radiotherapy portion defined, the appropriate tumor dose and over-all treatment time are chosen. The situation of the cancer and its extent then determine the apparatus, method, and other details of technique by which the required dose-time combination can best be administered.

During the course of radiotherapy continuing observations and frequent consultations are necessary. The general nutrition of the patient and emotional factors in both child and parents are important. Immediate radiation reactions such as nausea, vomiting, and local discomfort are seldom noticeable in children, but irritability, loss of appetite, and moderate pyrexia are perhaps more frequent in children than in adults. Children seldom seem to be bothered by the reactions in the skin and mucous membranes, but we are careful to avoid producing a moist skin erythema and always interrupt treatment for persistent "x-ray" diarrhea.

After the completion of the course of irradiation, personal observation at weekly or fortnightly follow-up visits is best, but if the patient's home is too far away, the radiotherapist should send a full account to the family doctor with detailed instructions for the care of radiation reactions, for example, the possibility of radiation pneumonitis, the hazards of a respiratory infection, or the harmful effects of sunlight on irradiated skin.

The management of radiation reactions in children does not differ from that in adults, but it is wise to give parents written rather than verbal instructions. We take pains to gain and keep the child's confidence by explanations appropriate to his understanding. The initial examination and first radiation treatment are all important; except for young babies, we never tie a child down on the x-ray couch, and only use a narcotic or sedative if repeated attempts at securing willing cooperation have failed.

The rule for parents is frankness but not gloominess, for the child readily senses their fears, and, furthermore, "spontaneous" cures and long-term remissions, though uncommon, do occur. The radiotherapist, having decided in consultation with the pediatrician and surgeon on the plan of treatment, should tell the parents what he hopes his treatment will accomplish, and not put them in the difficult position of having to decide

whether treatment is worth while. Most parents are better able to bear their loss, if the outcome is fatal, when they know that all possible means of therapy, whether curative or palliative, were fully considered and judiciously applied.

The following case illustrates the value of persistent adherence to a plan of action even if the result could perhaps be characterized as "spontaneous" regression.

CASE 1.—E. A., female, aged 4½ months, a patient of Dr. Edward Joyner, was admitted to Memorial Center Oct. 1, 1949, for treatment of an abdominal mass discovered in a routine examination one week previously. Laparotomy was performed after preliminary roentgenographic, urologic, and hematologic studies had been made. An inoperable retroperitoneal mass arising on the left side of the midline just superior to the left kidney and a greatly enlarged liver with diffuse infiltration by hard neoplastic tissue were found. A biopsy of the liver was made; the pathologic diagnosis of which was metastatic neuroblastoma.

She was given 0.4 mg. per kilogram HN_2 intravenously and started on radiotherapy. During a ten-day course she received a tumor dose of 1,064 r. On December 19 she was readmitted, showing proptosis, periorbital ecchymosis (Fig. 2), and a mass in the right flank. She received HN_2 (0.4 mg. per kilogram intravenously), and was given 1,030 r to the orbits. She was given Amethopterin at intervals during the following months but was often unable to tolerate the drug well due to vomiting. Her condition declined until March, 1950, when she become extremely emaciated, her proptosis increased, and eversion of her eyelids was marked. Her weight reached 7 pounds. Dr. Joyner continued to maintain her by transfusions and dietary measures through this highly critical period (Fig. 3). During the summer slow improvement began. In February, 1951, she was observed to have marked exophthalmos, periorbital ecchymosis, a mass 2 x 3 cm. in the midline of the abdomen, a liver 1 cm. below the costal margin, and a nonpalpable spleen (Fig. 4). Amethopterin in limited amounts continued to be given. In May, 1951, a right frontoparietal mass was treated with 900 r. Her weight at 2 years was 26½ pounds. A mass in the right parietal area was observed during the summer of 1951.

Fig. 2.—E. A., December, 1949, aged 7 months, weight 15 pounds 8 ounces. Periorbital and conjunctival ecchymoses from skull metastases.

Military orders took the family to Chicago, and she has been under the care of Dr. Mila Pierce since September, 1951. She was reported to be doing well in December, 1953, at the age of 4 years 8 months, although some visual and auditory impairment are noted.

TREATMENT OF COMPLICATIONS OF IONIZING RADIATION

Prophylactic.—As in any other morbid condition the therapy should be-

gin whenever possible with *prevention.*

Fetal Defects: The deleterious effects of ionizing radiation—mental deficiency, cerebral agenesis, among others—on the fetus are well known. It is therefore highly important that pregnant women receive diagnostic or therapeutic irradiation only after all considerations regarding the necessity for such procedures and the possible risks involved are thoroughly reviewed.

Fig. 3.—E. A., July, 1950, aged 14 months, weight 7 pounds. Progressive emaciation, some proptosis, ectropia, and periorbital swelling.

Fig. 4.—E. A., February, 1951, aged 21 months, weight 25 pounds. Improved nutrition, periorbital swelling, some ectropia, no proptosis.

Fig. 5.—E. A., January, 1953, aged 3 years 8 months. Continued general improvement, no ectropia; periorbital swelling still present.

Radiation Sickness: This is not a very common occurrence in children during the course of radiotherapy. It is seldom severe and it usually terminates promptly after completion of

the therapy. Pyridoxine (vitamin B_6), antihistamines (Elixir Benadryl), and Dramamine have been used in many of our intracranial, intrathoracic, and intra-abdominal cases, but their efficacy is not established.

Dermatitis: The early effects of ionizing irradiation on the skin may be mild enough to cause only a slight erythema. The reaction may rarely be severe enough, however, to produce sloughing within a period of fifteen days. Observation of the skin during the therapy will aid in determining unusual sensitivity. When sloughing has occurred lanolin or vitamin A and D ointment is used to keep the area lubricated and antibiotics are given orally or parenterally.

Late Effects: The list of possible late effects of irradiation is very formidable. The site affected and the nature of the injury determine the therapy. In the last few years the administration of cortisone during radiotherapy has been advocated for the possible prevention of pulmonary fibrosis following thoracic irradiation for various tumors of adult life. We have only used it in several cases in children, and the time period is too short to draw any conclusions about its value.

THE TREATMENT OF THE PRIMARY TUMOR

Surgery in Relation to Radiotherapy.—When there is no clinical evidence of metastases, and excision of the primary tumor seems technically possible, it often happens that an operation is performed first, and only after its partial or complete failure is radiotherapy considered. This sequence may have several disadvantages: first, tissue planes may be opened up and natural barriers (if present before operation) disrupted, permitting the dissemination of cancer cells in the area of operation and possibly even to distant sites; second, the potential value of irradiation is impeded, for its results depend so much upon an intact, healthy tumor bed; and third, unless there is close rapport between the physician concerned and the radiotherapist, the latter may have only a limited amount of information on which to form his estimate of the preoperative condition. The case for preoperative irradiation, after pathologic diagnosis, in borderline operable tumors is supported by the frequency of a high degree of malignancy in childhood cancers and by the not infrequent examples of postoperative recurrence, some of which may occur promptly.

It is of course absolutely essential in suspected malignant tumors that a histologic diagnosis be made, before *any* irradiation is given, preferably by aspiration biopsy. If an open biopsy is necessary for diagnosis, the radiotherapist should still be given the opportunity of seeing the patient beforehand. The surgeon undertaking the biopsy should on the one hand be capable of carrying out a radical excision should it be indicated, and on the other hand he should be aware of those radiotherapeutic considerations that may render a partial removal unnecessary or unwise. For example, Elliott Cutler taught that when the presence of a medulloblastoma had been verified by visual inspection, no biopsy should be taken because of the risk of thereby producing metastases in the spinal theca.

Chemotherapy in Relation to Radiotherapy.—The present-day results of

any *single* method of treatment of childhood cancer are so generally unsatisfactory that it is often desirable to use a combination of methods.

Coley's toxins, for long the sole agent in this field, has been largely supplanted by other chemical substances; their proper selection and administration are just as much the province of the chemotherapist as irradiation of the radiotherapist or excision of the surgeon, and the importance of teamwork from the outset cannot be overemphasized. The theoretical advantages of combined therapy are admittedly not yet proved by the one yardstick which can carry general conviction, namely, a statistically significant increase in five-year survival rates; nor is such proof going to be easily obtained while so many childhood cancers are suspected too seldom, and diagnosed and treated too late. This lack of proof applies to the simple combination of surgery and irradiation just as much as to the more complex combinations with chemotherapy.

The theoretical reasons for chemotherapy are: first, the noxious effect on cancer cells may be additive to that of irradiation; second, microscopic (subclinical) metastases may be inhibited or controlled; and third, recurrences may be delayed or prevented. Our general plan is to use nitrogen mustard or one of its analogues before irradiation, antimetabolites after irradiation, and hormones or Coley's toxins at times in some cases.

Radical Radiotherapy.—The term radical radiotherapy is used in the same sense as radical surgery is used to indicate that the treatment aims at cure. The radiation technique and tumor dose in what follows are precisely stated for the sake of clarity, but it must not be inferred that other techniques or different tumor doses are unsuccessful, for our own results are mediocre. However, there is such a lack of precision in the literature that very little guidance can be obtained from it. All the doses given are maximum tumor doses, calculated at the tumor center; the minimum dose (around the periphery of the tumor) is usually about 20 per cent less. The results of combined therapy have been stated in some instances.

Medulloblastoma

Technique: 1,000 kv. Two opposed lateral fields irradiating of the whole cranial cavity, 4,000 r in 4 weeks.
250 kv. Two long narrow posterior fields irradiating of the whole spinal theca, beginning during the second week of the cranial irradiation, 3,000 r in 4 weeks.

Results: Paterson[10] and Richmond[11] reported a five-year suvival rate of approximately 30 per cent. All other reports agree that although life is prolonged for about three years, local recurrence is the rule and cures are very rare.

Astrocytoma

Technique: 1,000 kv. Two opposed lateral fields irradiating the cerebellum. With 250 kv., add a third occipital field, 5,000 r in 6 weeks.

Results: No statistics available, but this tumor is both radiosensitive and radiocurable.

Other Intracranial Tumors: Not enough cases of the less common intracranial tumors have been irradiated with a consistent technique, so that the following statements are provisional:

Ependymoma should be treated in the same way as medulloblastoma, and is probably radiocurable.[12]

Hemangioblastoma requires a tumor dose of 3,500 to 4,000 r in 4 weeks, and is possibly radiocurable.

Craniopharyngioma probably requires a tumor dose of 6,000 r in 6 weeks to slow down the reaccumulation of fluid in the cyst and to inhibit the proliferation of the epidermoid cells. We are not aware of cured cases of craniopharyngioma by irradiation alone.

Retinoblastoma

Techniques: 1. Radium applicator sutured on the sclera, 4,000 r (calculated at the summit of the tumor) in 8 days.
2. X-ray therapy.

Results: Stallard[13] reported on 29 patients, all living, 24 with vision and 5 blind. Reese[14] reported on 53 patients treated with x-rays; 41 are living, 25 with vision and 16 blind; 12 are dead. Implantation of radon seeds is of historical interest, since it first demonstrated the radiosensitivity and curability of retinoblastoma with preservation of vision.[15]

Neuroblastoma

Technique: Intravenous nitrogen mustard, 0.4 mg. per kilogram. X-ray therapy, 2,500 to 3,000 r tumor dose in 3 weeks.

Results: About 22 per cent three-year survival rate.[16]

Wilms's Tumor

Technique: Transperitoneal nephrectomy, immediate postoperative x-ray therapy, tumor dose approximately 3,000 r in 20 days.[17]

Results: Under 1 year of age, 80 per cent two-year survival rate. Over 1 year of age, 43 per cent two-year survival rate.
Collected series about 20 per cent three-year survival rate.[18]

Other Methods: For large, possibly inoperable, tumors, preoperative irradiation (2,000 r in 10 days) seems logical, since marked regression usually results, but Gross and Neuhauser are convinced that it carries an increased risk of pulmonary metastases.

Rhabdomyosarcoma

Technique: X-ray therapy first, 4,000 r in 5 weeks; if tumor does not completely disappear, either radium implant or excision.

Results: No statistics available, but it is known that primary excision without irradiation is often followed by local recurrence.

Spindle-cell sarcoma

Spindle-cell sarcoma and other types of sarcoma occurring in soft tissues are often congenital, and (unlike the analogous sarcomas in adults) are usually radiosensitive and at times radiocurable.

Technique: X-ray therapy, 3,000 r in 3 weeks.

Results: The prognosis is guarded but gratifying results occur.

CASE 2.—A. T., female, aged 2 months, a patient of Dr. George Pack, was admitted to Memorial Hospital Dec. 7, 1934. Shortly after birth a swelling of the lower third of the left leg was noticed, and it increased in size to occupy an area 7 cm. in length; the circumference of the leg here was 16 cm. Roentgenograms showed a soft part shadow, osteolytic areas in the tibia, and periosteal reaction. Biopsy was performed and the diagnosis on the tissue removed was unclassified sarcoma. A total tumor dose of 3,750 r was given through two ports in 18 days. She has remained free of disease for 19 years. The problem in gait caused by shortening of the treated leg has been corrected by an epiphyseal closure of the right leg.

Malignant Teratoma and Embryonal Carcinoma

These tumors are considered together because their usual origin is from totipotent germinal cells. While quite radiosensitive, they are not necessarily radiocurable, so that combined surgery and radiotherapy appears preferable.

Technique: X-ray therapy, 3,000 to 4,000 r in 3 to 4 weeks.

Results: The prognosis appears to be better in infancy than in childhood.

Ewing's Tumor of Bone

Technique: Intravenous nitrogen mus-

tard, 0.4 mg. per kilogram.

X-ray therapy (to the whole length of the shaft if in a long bone), 3,500 r in 3 weeks.

To be followed by "prophylactic" x-ray therapy to the lungs; 1,000 kv., 2,250 r to the whole chest in 3 weeks, tissue dose calculated at the midpoint between the anterior and posterior fields; accompanied, or possibly followed, by a course of Coley's toxins.

Results: Only 4 per cent survival rate in the series reported by Coley, Higinbotham, and Bowden.[19]

Reticulum-cell Sarcoma of Bone

Technique: Intravenous nitrogen mustard; x-ray therapy 3,500 r in 3 weeks; possibly accompanied or followed by a course of Coley's toxins.

Results: Probably about 30 per cent long-term survival rate; prognosis is uncertain because (a) there have been late recurrences and metastases after five years' freedom from disease, and (b) cases histologically indistinguishable from those with a favorable outcome and with a satisfactory response to irradiation may nevertheless soon develop generalized metastases.

THE TREATMENT OF METASTASES

Metastases in Lymph Nodes.—Since regional lymph node metastases occur in many childhood cancers, the regional lymph nodes are included in the irradiation of the primary tumor whenever feasible; for when separate fields have to be used for the irradiation of the primary tumor and of adjacent metastatic lymph nodes it is very difficult to ensure homogeneous dosage; where adjacent fields meet, zones of underdosage are more likely than zones of overdosage, but either may result in persistence of malignant cells with ultimate clinical recurrence.

Blood-borne Metastases.—The distribution of blood-borne metastases is not a purely mechanical process, for osseous metastases are common in neuroblastoma without any evidence of pulmonary metastases even at autopsy, and sometimes occur with other tumors such as Wilms's tumor and Ewing's tumor of bone. It follows that some tissues would appear to be able to prevent tumor emboli from developing into clinically evident metastases, and hence the presence of distant metastases does not invariably denote incurability, for treatment may aid the normal tissue to overcome the metastatic cancer. However, the detection of an isolated blood-borne metastasis usually foretells the later appearance of multiple metastases, so that whenever indicated we use systemic agents for the control of undetectable metastases in conjunction with irradiation of the obvious metastasis. Sometimes there is reasonable doubt whether a second tumor is a metastasis or a second primary tumor, for example, bilateral Wilms's tumors of the kidneys, an osteogenic sarcoma of the radius eighteen months after amputation for an osteogenic sarcoma of the tibia without any evidence of pulmonary metastases, or a second reticulum-cell sarcoma of bone without intervening pulmonary metastases. And sometimes there are two distinct conditions, such as a 3-year-old boy with an adrenal cortical tumor who developed a malignant melanoma, or another one with Hand-Schüller-Christian's syndrome who developed a medulloblastoma. The radiotherapy of metastases or apparent metastases may therefore sometimes justifiably be radical with intent to cure.

Hepatic Metastases: Metastases in the liver may be the only evidence of disease in abdominal neuroblastoma;

spontaneous disappearance as well as radiation cures are known. Other intra-abdominal and retroperitoneal cancers may also give rise to metastases confined to the liver. Since the normal liver easily tolerates radiation-dose levels of the order of 3,000 to 4,000 r without any impairment of function, it is usually justifiable to attempt the cure of hepatic metastases by irradiation.

Pulmonary Metastases: Although the evidence is as yet incomplete, we think that normal lung tissue in children can tolerate 2,000 r without any evidence of damage; in the range of 2,000 to 3,000 r a patchy pneumonitis develops after irradiation, but usually resolves, apparently completely, within four months; above 3,000 r resolution is uncertain and some degree of permanent pulmonary fibrosis with impairment of function is probable.

CASE 3.—J. R., aged 6½ years, was admitted to Memorial Hospital Nov. 20, 1951, for treatment of Ewing's tumor of the left tibia. A tumor dose of 2,364 r was given in 14 days, the first dose being preceded by 0.4 mg. per kilogram of HN_2 intravenously. In January, 1952, he was given "prophylactic" pulmonary irradiation, dose of 2,250 r. In April, 1952, a roentgenogram of the chest showed areas suggestive of metastases. These subsequently cleared without any therapy and were considered to be pneumonitis, probably due to irradiation. In August, 1953, the lungs roentgenographically were still normal and no other signs of recurrence were found.

In the majority of childhood cancers, when pulmonary metastases develop they are multiple and bilateral or soon become so; in such cases, if the primary tumor is controlled and there are no metastases elsewhere, we irradiate the whole chest to a minimum tissue dose of 2,250 r in two to three weeks. There is evidence that radiotherapy is sometimes curative,[20] but usually it causes only temporary disappearance of the metastases for a few months.

In some types of cancer, for example, embryonal carcinoma and carcinoma of the thyroid, isolated pulmonary metastases are not always the forerunner of multiple metastases. We therefore sometimes irradiate isolated pulmonary metastases through small fields, and in such cases give a tumor dose of 3,000 to 3,500 r (without risk of subsequent impairment of respiratory function) because the area of fibrosis is small.

It is very important that every patient who has had pulmonary irradiation should avoid superadded infection, and if such respiratory infections occur they must be taken seriously and energetically treated. In adults we have not found cortisone a reliable agent for the prevention of radiation pneumonitis or fibrosis.

Skeletal Metastases: While hepatic metastases are certainly sometimes curable by radiotherapy and pulmonary metastases occasionally, skeletal metastases always indicate a poor prognosis, and particularly so if the aspirated sternal or iliac marrow contains tumor cells; hence we regard irradiation of skeletal metastases as solely palliative, and in most cases a tumor dose of 1,000 to 2,000 r is sufficient for relief of pain and for the conversion of an osteolytic lesion into an osteosclerotic area.

Intraspinal Metastases: Compression of the spinal cord is due to leptomeningeal metastases from certain intracranial tumors, and to extradural metastases or extension in malignant lymphoma, neuroblastoma, and some

other childhood cancers. It is always a radiotherapeutic emergency, for irradiation within a few days of onset generally results in complete functional recovery. The lesions may be multiple, so that we usually irradiate a generous length of spinal cord to a tumor dose of about 3,000 r in three weeks; the first few doses are small, 50 to 100 r, so as not to risk further cord compression through swelling of the tumor.

THE TREATMENT OF MALIGNANT LYMPHOMA AND RETICULOENDOTHELIOSIS

The use of radiotherapy in the management of the generalized affections of the lymphoreticuloendothelial system is mainly directed toward the relief of symptoms and the prolongation of comfortable life. In general, therefore, only small or moderate doses of radiation are indicated, which may destroy some of the pathologic cells and alter others in the direction of greater differentiation, but seldom completely sterilize the irradiated area. There are, however, occasions when higher radiation doses (comparable to those used in the "radical" radiotherapy of localized cancers) may be useful: for example, in Hodgkin's disease presenting in a single group of lymph nodes, sterilization of the area may be attempted in the hope of a long remission or even of apparent cure.

Acute Leukemia.—Now that partial or complete temporary remissions are being frequently produced in acute leukemia by chemotherapy, complications due to leukemic infiltration of various organs are more often observed, and some of these have proved amenable to irradiation. Meningismus, papilledema, and oculomotor palsies; involvement of spinal nerve roots and compression of the spinal cord; leukemic masses and ulceration in the mouth and nasopharynx; superior mediastinal compression; uremia from renal infiltration; jaundice from hepatic involvement; these are some of the conditions which have been relieved by x-ray therapy. As regards dosage, we usually begin with 50 to 100 r, and have found that with daily treatments a total dose of 300 to 600 r is generally required for improvement.

Chronic Myeloid Leukemia.—In the few cases of chronic myeloid leukemia that we have observed in children, the treatment of choice appears to be irradiation of the spleen, as it is in adults. With x-ray therapy at 250 kv., anterior, posterior, and left lateral 10 × 15 cm. fields are used in rotation; starting with a dose of 25 to 50 r, the dose is increased about every third day, using the blood picture as a guide, until it reaches 100 or 150 r daily. A favorable response comprises an increasing red cell count, a rising hemoglobin, a decreasing white cell count, and diminishing numbers of immature cells. A falling red cell count and a diminishing platelet count indicate a need for caution, either by reducing the x-ray dose or by a temporary interruption of treatment. The total peripheral white cell count is not the best guide either to the daily dosage or when to end the x-ray course, for with a total of, say, 6,000 white blood cells per cubic millimeter there may still be many myeloblasts and myelocytes; we regard a satisfactory end point as absence of myeloblasts and less than 2 per cent myelocytes in the differential count. A lengthy remission may

be anticipated if the bone marrow picture returns to normal, which is also of interest as one of the few instances when local irradiation apparently exerts a systemic effect.

Hodgkin's Disease.—In apparently localized Hodgkin's disease in children, intensive treatment aiming at permanent control seems justified, but our experience is insufficient to know whether it is as safe as in adults. For example, in a 12-year-old girl with cervical and mediastinal nodes, intravenous nitrogen mustard (0.4 mg. per kilogram of body weight) and an x-ray tissue dose of 3,000 r in ten days was given, and she has remained well for two years, but in a 8-year-old boy with bilateral cervical nodes, after the same dose of nitrogen mustard and an x-ray tissue dose of 2,250 r in eight days, the radiation reactions in the skin, mouth, and pharynx were so severe that the patient was critically ill for over two weeks.

In multifocal and generalized Hodgkin's disease, x-ray therapy is directed toward the relief of symptoms and temporary control of the disease in localized areas; for these purposes a tissue dose of 1,000 to 1,500 r in a period of one to two weeks is usually adequate. Although most of the clinical manifestations of Hodgkin's disease are referable to the soft-tissue portion of the reticuloendothelial system, the bones also are frequently involved, and bone pain may precede radiographic evidence of bone destruction. Recognition of the symptom and early x-ray therapy are particularly important in the case of the vertebrae, for both collapse of the vertebra and compression of the spinal cord through extradural spread can be prevented.

Letterer-Siwe Syndrome.—The nosology of some generalized, or potentially generalized, affections of the reticuloendothelial system is ill defined, but at least some cases of Letterer-Siwe syndrome and some cases of Hodgkin's disease are indistinguishable in their late stages from generalized reticulum-cell sarcoma. Their uncertain pathology is matched by wide variations in their radiosensitivity, so that each case is an individual problem. In Letterer-Siwe syndrome chemotherapy is receiving more support as the primary method of treatment, but occasionally regression of a small tumor after an x-ray dose of 1,000 r occurs, and in such cases irradiation of a large volume such as the abdomen or thorax may be justified.

Hand-Schüller-Christian Syndrome.—The skeleton seems unique among the systems of the body in manifesting lesions which may occur in a solitary focus, or in multiple but localized foci, or as a generalized affection of the whole skeleton. The least uncommon example in children is the solitary eosinophil granuloma of bone, its multiple occurrence in several bones (not necessarily simultaneously), and Hand-Schüller-Christian syndrome.

The osteolytic lesions of Hand-Schüller-Christian syndrome are radiosensitive, and whether x-ray therapy is given because of extensive bone destruction or for an overlying soft-tissue swelling or for proptosis, a dose of 1,000 r over a period of six or eight days is usually adequate. In the calvarium reossification is often slow and incomplete, but in most other bones it is well advanced within two months of irradiation.

The solitary eosinophilic granuloma of bone responds to x-ray therapy in a similar manner.

The pathologic diagnosis of many lesions of bone from material obtained by aspiration biopsy is difficult. An eosinophil reaction may be the predominant feature of a number of different lesions. An open biopsy may also fail to secure representative material, and excision of the complete osteolytic lesion may often seem unjustifiable. Nevertheless definitive therapy mut be deferred until a diagnosis is established.

RADIOTHERAPY IN NONMALIGNANT CONDITIONS

The present state of knowledge as to the late effects of even a small dose of radiation (say 400 r) to a small area (say 10 sq. cm.) of the body of a child does not permit us to say that it is completely safe. Although irradiation often appears to be the treatment of choice for a variety of benign conditions already memtioned we therefore feel that it should not be used if there are acceptable alternative methods of treatment. Most radiotherapists believe that a single "threshold erythema dose" of radiation is devoid of risk, yet it must be recognized that the number of children who have been followed for even as long as twenty years after irradiation of a benign lesion is far too small for any certainty in the matter. In a subject which is still controversial, it would seem best for the radiotherapist to err on the side of caution, and to leave to the pediatrician the assessment of those conditions, whether medical, psychological, or cosmetic, which he may regard as indications for radiotherapy of benign lesions.

Dosage for "Benign" Lesions

Cavernous hemangioma: 60 to 100 kv., 400 r, single dose.

Keloid: 60 to 100 kv., 400 to 800 r, single dose.

Lymphangioma (cystic hygroma, macrocheilia, etc.) 100 to 130 kv., fractionated dosage, 800 to 1,200 r in 10 days.

Lymphoid hyperplasias: 150 to 250 kv., fractionated dosage, 200 to 500 r in 2 weeks.

Aneurysmal bone cyst (hemangioma of a vertebra, for example): 250 kv., 1,000 to 1,500 r in 1 to 2 weeks.

Papillomatosis of the larynx: 250 kv., 1,000 r in 6 days.

SUMMARY

1. Radiotherapy is one of the most formidable therapeutic agents available for the treatment of many tumors of children.

2. Certain elementary therapeutic principles governing the treatment of any morbid process also apply to the use of radiotherapy:

a. There must be positive indications for the recommended therapy.

b. The physician must be thoroughly acquainted with the procedure or agent used in the therapy.

c. The limitations as well as the encouraging possibilities of the therapy should be known by the child's family.

3. An accurate appraisal of the value of ionizing radiation cannot be made now. Only after many more cases are treated earlier and end results of fifteen or more years are reviewed will this be possible.

4. There is sufficient evidence now available to recommend more extensive use of radiotherapy in the neoplastic diseases of children.

5. Current techniques in the use of ionizing radiation in children are based chiefly upon the limited radiotherapeutic experience in the field of pediatric oncology. It is not to be expected that uniformity of opinion would now exist or that changes and improvements in methods will not occur as experience widens.

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Psychologic Aspects of Pediatrics

INITIAL COUNSELING OF PARENTS WITH MENTALLY RETARDED CHILDREN

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THE problem of how much, when, and how to tell the patient or his family is an ever-present one in medicine. The situation varies with the diagnosis, the nature of the patient or family, and the personality of the physician. When the diagnosis is clear-cut, the prognosis favorable, the patient or family free from great anxiety, and the physician confident of his therapy, the problem of informing the patient or family either does not arise at all, or else permits of ready disposition. The concern of the present paper is with mental deficiency, a situation in which none of these favorable factors prevails. Here the prognosis is almost uniformly poor, the etiology only infrequently ascertainable, the parents regularly anxious, and the physician seldom confident of a therapeutic regimen.

The anxiety of the parents is of particular concern to the physician who must tell them his diagnosis* of mental deficiency. There are a number of reasons for this anxiety. To begin with, there is an awareness of the long-term implications of the diagnosis, and of the extremely limited therapeutic outlook. Another reason is the widespread awe of the "mental" as against the "physical" in human malfunction. However far we prefer to feel we have moved from the era of demonology, an irrational fear of intellectual deficiency is still manifest precisely because it is "mental." It must also be noted that there is seen, with extraordinary frequency, a marked guilt reaction on the part of the parents. The sources of the guilt feelings are complex and outside the scope of this paper, but their manifestations are familiar to the physician who has dealt with the parents of retarded children. Finally, as Doll[1] has stressed, the core of any definition of mental deficiency is social incompetence, and much of the parental anxiety reflects the social stigma inherent in severe and prolonged social incompetence. Abel[2] has recently written: "The mentally retarded is a deviant who is perhaps treated with greater rejection and less respect by parents, teachers and the community than is any other deviant, perhaps with the exception of the person with Hanson's disease." Certainly a number of additional diseases provoke rejection and loss of respect by family and community, but it remains true that the characteristic attitude of the community to the mentally retarded child operates to heighten the anxiety of the parents of the child.

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*Although mental deficiency is not, in the usual sense, a "diagnosis," it is in most instances so considered and is used in this manner in the present paper.

At the same time much can be done precisely at the time the diagnosis is presented to the parents to reduce this anxiety and to promote a more accepting and constructive attitude toward the child. It is the thesis of this paper that the initial counseling of the parents is of critical importance in this regard, and that appropriate handling by the physician can turn a potentially devastating experience into the foundation for a satisfactory adjustment to the problem and to the child.

PROCEDURE

The National Association for Retarded Children initially stimulated this study and cooperated in the procedure. Members of the N.A.R.C. who were themselves parents of retarded children were asked to communicate with me with regard to the circumstances of their first learning of the diagnosis, their reaction at the time, and their feelings about whether the situation had been well or poorly handled. Eighty-five letters were received from parents scattered over twenty-three states and Canada. The contents of these communications were then tabulated and form the basis of the discussion presented below.

Several considerations render the data unsuited for normal statistical handling. These experiences are presented as reported by the parents, with no independent data available as to what the physician actually said or did. In addition to the misconceptions and distortions seen with some frequency immediately after contact with a physician, there is here the added problem of an interval of from a few months to several years having elapsed between the actual contact with the doctor and the report of this contact by the parent. Again, these are unusual parents in that they have been able to accept their retarded child at least to the extent of identifying themselves with the membership of the National Association for Retarded Children. The ability to write about the initial experience of being informed of the diagnosis of mental deficiency in their child is a further differential factor in this regard. One parent wrote, ". . . a person cannot sit down and write of this experience without opening old wounds. I think you would get more information through interviews than letters, for somehow it is easier to talk than to write." Finally, it is likely that experiences felt by the parents to have been poorly handled by the doctor would be more likely to prompt a letter than experiences felt to have been adequately handled. It must, therefore, be stressed that the letters cited are by no means offered as reflections of what physicians generally do in handling this problem, nor is it the intent to offer a tabulation of how representative parents react to being informed of the diagnosis of mental deficiency. Rather, the reported experiences have been analyzed for their individual content, and common concerns have been extracted for discussion as suggested areas of interest to the physician faced with parents with retarded children. These are presented below, and are then compared with techniques for handling the initial counseling of parents with retarded children proposed by three recent contributors to the literature in this field.

RESULTS

The Attitude of the Physician.—

1. A striking number of letters (thirty-three of the eighty-five) refer to the importance of the attitude of the physician. A representative letter noted: "Dr. J. was superb in his telling of Steve's limitations.... Mainly, the points I remember were of course his gentle treatment of us, his exquisite choice of words so as to avoid the obnoxious ones...." Another wrote: "We shall be everlastingly grateful to our young pediatrician for his skillful, sympathetic handling of our case. He took as much interest in us as he did in our child and spared us what may have been a dreadful shock." The converse experience is reported by another parent as follows: "When his prophecies failed to materialize within the allotted time, he sent us to a very distinguished neurologist-psychiatrist. This man pronounced the accurate diagnosis with a hard, cold, almost surgical economy of words and feelings. To put it mildly, he was brutal. My wife and I walked through the streets of Brooklyn, weeping openly." The significance to the parents of the attitude of the physician is reflected not only in the frequency with which it is mentioned, but also in the degree of concern which is expressed. One parent reported that her doctor had commented about her mongoloid daughter that ". . . they make nice pets around the house." Another wrote: "This doctor was a woman, and I didn't have my child with me at the time. She asked me many questions about her training and eating habits, then she asked me about her speech. When I said she didn't talk, she told me I should put her away and forget I ever had her, unless I wanted to limit myself to a dog's life. At least a dog could bark, she told me. . . . Every time I think about this doctor, I think how much more I have than her, and that is love for human beings." One letter made it clear that the parent was not seeking maudlin sentimentality; "I was taken back to my room, and about twenty minutes later my doctor came in and the tears were running down his cheeks. He said there was something terribly wrong with my baby. He couldn't tell me at first, but finally told me that my baby was the type known as mongoloid. . . . My doctor had a compassionate heart, but it just seems to me that he did not have the right psychological approach. I was terrorized over the situation and remained so for about three years."

The concern of these parents with the attitude of their doctors is, of course, not unique to the field of mental deficiency. It is my impression, however, that few diagnoses provoke more anxiety in the physician than feeble-mindedness. A meaningful study remains to be done in defining the sources of doctors' attitudes toward mental deficiency. In any case, it is apparent that some parents react with great sensitivity to the warmth or coldness, the gentleness or harshness, the acceptance or rejection in the attitude of the doctor.

2. Twelve of the letters received from the parents comment upon the thoroughness of the study which preceded the announcement of the diagnosis. Several shared the direct comment of the mother who wrote, "I, as a thinking parent, was not content with anything less than a complete study

of the child." Another wrote, "Dr. B's statement on hearing my story was, 'I cannot say from this one examination just what is wrong, but if it were my child I would make certain tests.' . . . Blood tests were made and x-rays taken . . . the consensus of neurological, psychological and medical examinations agreed with her tentative diagnosis." Another parent, reporting a less favorable experience, wrote, "A lot of the shopping around that doctors deplore would be avoided if doctors would take patients into their confidence and not act threatened when a consultation is requested." A less bitter report by another parent was, "Dr. L. saw her for five minutes. . . . He told us gently enough that she would never be able to assume adult responsibilities and that there was a theory that the same kind of lesions as she had on her face, that Dr. B. had called adenoma sebaceum, probably were inside her skull and pressed on her brain. . . . We should have accepted what he said but we felt that he had not seen her for long enough. . . . Dr. C., a psychiatrist friend of mine, told me that one of the things he had learned with experience was not to give patients a quick diagnosis. Even if he knew what was wrong, he said, he went through the motions of more examinations because that gave people more confidence that he was not judging hastily."

It is, of course, obvious that not all clinical types of mental deficiency require equal investigative effort. Further, and precisely in cases in which diagnosis is immediately apparent, parents will recognize the perceptiveness of the physician and will be pleased that prolonged study was not required. Certainly, too, the suggestion that the physician who knows the diagnosis and prognosis make a pretense of thoroughly examining the child must be rejected. It remains true, however, that in many instances the special skills required for an inclusive evaluation of a retarded child exceed those possessed by the individual practitioner. Pediatrics, neurology, radiology, psychology, psychiatry, and orthopedics each may contribute. The physician should certainly be prepared, where indications exist, for consulting specialists in these and other fields, to explain the need for these consultations, and to utilize all available relevant professional resources toward the end of complete diagnosis.

3. Related to both the attitude of the physician and the thoroughness of the study preceding the diagnosis is the problem of the kind of information requested by the parents. In this regard, there are several interrelated problems. As is so often the case in the communication of technical information to lay persons, the problem of intelligibility is relevant. One parent wrote, "I feel that it is the doctor's duty to have the parents in for a discussion of what the full meaning of their diagnosis is. Instead, in their well-meaning way, they left us with a mumbo-jumbo of medical terms that I had to find a medical dictionary to look up the meaning." Another wrote of being sent by the family doctor to a specialist, who ". . . gave us what amounted to me to a great deal of double talk in medical terms that were above my comprehension." Concern with the content of the doctor's statement was more prominent. Eleven letters made reference to the fact that the doctor

had stressed the negative aspects of the picture to the total exclusion of any assets in the child. One parent wrote, "I believe that when the doctor tells parents the child is defective he should point out the fact that it is possible to maintain a normal family life with such a child . . . and not point out the negative side so readily, which is done most of the time." Another parent listed some of the current accomplishments of her 5-year-old daughter, and added, "The thought has occurred to me many times, but there is no way of knowing, that it might have been a different story for me if the doctor had told me a few things like that . . . just knowing that they do act like human beings would have helped, I think." A third parent wrote, "Tim is 5 years old now, very lovable, and he can say several words and even group a few together. He can ride a bicycle. . . . All of the doctors who saw Tim were kind, but not one of them gave one word of hope or reassurance." A related problem was the concern of the parents for more information with regard to the prognosis and management of the child. Several expressed similar views with the parent who wrote, "Doctors should be supplied with more material so they could advise you . . . on the proper ways to rear a retarded child, so that you will not expect more of the child than he is capable." Another wrote, more emphatically, "If I were to summarize what we would want, it is . . . an explanation to the parents of what [diagnostic procedures] has been done . . . what positive conclusions can be drawn, what uncertainties remain, what general prognosis can be made. . . . The physician should give continuing, positive advice, well founded, and of a practical nature, on the day-to-day handling of problems."

It is here again pertinent to add that parents present a wide range of capacities for accepting and understanding the doctor's discussion. One must agree with the parent who wrote, ". . . when a husband is a PH.D. and the wife a college graduate, I think the doctor should lay the books on the table. He makes himself look foolish when he doesn't." At the same time, initial counseling must also be provided to the parent who wrote, "My reaction to the knowledge of my child's retardation was to lead an army, all alone if necessary, to help her live a normal life." This parent never did get beyond the expression of her powerful feelings of protectiveness for her child to describe the actual experience of being informed of the diagnosis. No single formulation of content can hope to serve so varied a population. A second point to be stressed in this regard is that the physician is being asked to provide information in fields in which he only rarely attains competence—child rearing, and education of retarded children. A technique reported upon favorably by the parents is of providing appropriate literature at the time of initial counseling. Several excellent pamphlets and books are available, and a bibliography for such purposes may be readily obtained by writing to the National Association for Retarded Children.* An additional suggestion of even wider applicability is for the physician to direct the parents to the local council for retarded children. Most units maintain programs directed

*Box 85, Wall St. Station, New York, N. Y.

precisely toward answering these questions, and at the same time serve to integrate the parents into the wider community aspects of the problem of mental deficiency.

4. A theme which appeared in twenty-two of the eighty-five letters written by the parents was the positive role played by religion in their adjustment. In most instances there was only a brief reference to the role, but several parents devoted considerable emphasis to this source of help. One noted, "It was really through the church that I gained two important insights: one, that we looked at things as punishment which might be our own guilt feelings . . . two, in connection with the Bible story of the man born blind, that these things were not a reflection on the parents, but could be used as a means of helpful endeavor."

In this connection it would appear that the physician might extend the collaboration with the minister, priest, or rabbi, certainly not infrequent in many areas of work, to the initial counseling of parents with retarded children when this appears to be indicated.

Institutional Care.—

5. The most bitter expression of feeling by the parents concerned their being advised to institutionalize their retarded children. This subject was approached in widely varied ways. Some, concerned with the frequency with which the advice to institutionalize the child was given, wrote on the factors within the doctor which they felt to be responsible. One parent felt that, "Medical doctors work with so much sick tissue that they think everything defective should be scrapped." Some parents remarked on the lack of factual information concerning institutions possessed by the doctors urging this disposition. One wrote, ". . . this has come up with other doctors; they do not know the institutional setup and do not take the trouble to find out what facilities are actually available and suitable for the child, nor do they refer parents to positive sources of information on these topics. One psychiatrist recommended the W. . . . School [a very expensive private school] to the wife of a machinist. In our case, the recommendation of Letchworth Village [a New York State institution] to New Jersey residents was quite frustrating." Fifteen parents commented on the attitude of the physician toward institutionalization as one of finding some place to "put away" the child, rather than as a positive procedure in the management of the child. A rather typical statement by one parent read, "He folded his arms across his chest and without batting an eyelash said, 'You're wasting your time. The only thing to do with this child is to place him in an institution.'" Another parent wrote, "The doctor there . . . advised that we should put him away and forget about him. I have never in my life heard such a cruel sentence." Five parents characterized the doctor's attitude toward institutionalization as demanding. One wrote, "I can supply you, practically verbatim, with the interview we had with the doctor . . . and with our reactions over that week end when we thought our boy would be snatched away to an institution in a very short time." Twelve letters referred scornfully to advice for immediate institutionalization and

then described a currently adequate home adjustment. One parent wrote, "Each time we went to the doctor he would ask us if we had taken out the papers yet, and when we said no he would harass us further. . . . Our boy walked at 3, stood up alone and walked on his birthday! Were we ever surprised! You can imagine our joy! It took us quite a time to really accept him for the child he was, and to see he would never be the child we would have liked to have him be. He is a happy, well-adjusted and self-sufficient child." The parent quoted above as interpreting the advice to institutionalize her child as a "sentence" went on to write, "My boy is now 6 years old. He goes to D. . . . School. He is talking very well and can carry out all the orders I give him in the home. He is sweet, very affectionate, and I guess the dearest little soul on this earth as far as his mother, daddy, and sister are concerned." A less frequently voiced complaint about advice to institutionalize concerned the timing; characteristic was the statement, "I would say that a doctor should take it in easy stages in telling a parent. Tell them the child is retarded, yes, but don't go into a long talk about institutions. A parent is absolutely in no condition at the time of the initial shock to hear a verdict like that."

These statements serve to emphasize a most important area of concern to the physician who must tell parents of the existence of mental deficiency in a child. The decision to institutionalize a retarded child is complexly determined by the nature of the child, the available institutions, the parents, the siblings, and the timing of the procedure in the light of all these factors. The role of the institution in the management of the retarded child is variable; the proportion of actual training and of sheer custodial care will vary with the adequacy of the institution as well as the abilities of the children. Institutionalization is not a disposition to be cavalierly arrived at, nor one to be callously recommended.

When to Inform Parents.—

6. Among the parents who commented on the point, there was substantial agreement concerning the question of *when* they should be told of the diagnosis. Eighteen of the letters reported at least one, and generally several, experiences of being told their child would "grow out of it." Thirteen of the letters make the specific complaint that the parents should have been told earlier: "He [the consultant pediatrician] also told us to go back to our family doctor and not to go chasing after miracles. At the time I was very depressed and bitter toward our family doctor. Since then we have gone back to him, but there is still a little resentment because he didn't tell us himself when he first suspected the baby was retarded." Another wrote bitterly, "I continually asked my pediatrician why Brian was so slow—in sitting up, in standing, in walking; if there was any chance that his physical slowness would be accompanied by mental retardation. Always I got a placating, 'No, he is just slow and will catch up.' There was no effort to refer me to a psychologist or psychiatrist for testing and advice. Do not the doctors know the signs of mental retardation and deficiency, or are they just afraid to tell us?" Several parents described the converse experience; one wrote,

"I'm glad I knew from the start. Worry would have been worse." Another wrote, in a similar vein, ". . . learning the results of his tests was at the same time a tremendous blow and a tremendous relief from worrying and wondering just what, if anything, was wrong." In a few instances (five letters) a stronger feeling is expressed on this matter, in terms of the feelings of inadequacy developed by the parents. One mother reported, in dialogue form, a series of conversations with various doctors in which she asked about specific developmental lags and was continually reassured that the child merely needed more time, ". . . until I got to the point of feeling that I was a neurotic mother —a completely inadequate one—with no one paying any attention to me, not even my own husband." Only one letter expressed support for a delay in being told the diagnosis. This mother learned that she had given birth to a mongoloid child through a tragedy of errors in which the husband, obstetrician, and pediatrician each thought one of the others had told her, and, therefore, greeted her successively on the morning after the delivery with expressions of sympathy. She wrote, "I do not think a mother should be told until she has had at least two weeks to recuperate from the actual birth of the child."

In the matter of the timing of discussions and advising institutionalization, the parents contributing letters to the present study are particularly unrepresentative samples of the population with which the physician must deal. First, these *are* parents of retarded children, and one would have to raise the question of how vigorous a protest against doctors who gave incautious diagnoses of mental deficiency could be culled from parents with children who did "grow out of it." Certainly, the anguish caused by needlessly alarming such parents can equal or exceed the despair of the parents contributing to this report. Again, these are parents who have accepted their children at least to the point of joining member units of the N.A.R.C. Denial is then not prominent in their collective defenses against the impact of the diagnosis, and denials on the part of their physicians are condemned. No conclusion concerning actual practice is, therefore, warranted from the letters in this regard. However, it may be emphasized that the letters express concerns which are central to good clinical practice. The task of the physician is to become fully skilled in developmental diagnosis, so that clear indications of mental deficiency are not relegated to the lower end of the normal range. It is likely that the anxiety of the physician, rather than a lack of knowledge concerning developmental norms or a lack of faith in the capacity of the parents to accept the diagnosis, prompts some of the counsel for waiting for the child to "grow out of it." It is the further task of the physician to recognize and avoid such motive for his counsel.

A number of additional issues were raised by the parents who submitted letters, but represented unique interests of these separate parents and have, therefore, been omitted from this discussion.

DISCUSSION

The initial counseling of parents with retarded children has received

scant attention in the literature, particularly in the nonpsychiatric literature. Jensen[3] has recently dealt with this problem. He emphasizes that the gravity of the situation is better appreciated when it is realized that between one and four million *families,* rather than individual children, are involved. He feels that errors made by physicians in handling the problem may increase the suffering of the parents, and lists as the three most frequent errors: "(1) Delay in defining the problem early in the patient's life"; "(2) encouragement of parents by holding out false hopes, which naturally results in disillusionment later"; and "(3) too much direct advice and/or urging adoption of a specific plan—too often institutionalization." He feels, with regard to the latter point, that the doctor may fail to take into account "the strong emotional ties that most parents center in the mentally handicapped person," and may thus invite resistance to his diagnosis. He lists as basic steps in the contact with parents: providing ample time; thoroughly studying the child; exercising care in the language used to the parent; respecting the right and the responsibility of the parents to determine disposition; maintaining an objective and analytic attitude; and using trained but not overaggressive psychologists and social workers for such contacts. In his final interview with parents he offers the most likely explanation for the retardation, and offers four solutions: home care, boarding home, private school, and state school. He is careful to state the latter choice as taking advantage of the opportunity and facilities offered by the state. He stresses the actual saving of time which results from his procedure, both through a reduced need by the parents to "shop around," and an increased capacity for understanding the child and lessening destructive pressures on him.

Doll[1] notes that the parent's question, "Is my child feeble-minded?" is really meant to be, "How feeble-minded is my child?" He sees the parents as asking four basic questions: "How is my child from the standpoint of suspicion of mental deficiency? What is the cause of it, if present? What have I to look forward to? How long will it take and what shall I do in the meantime?" He introduces a concept which he terms "the cluster aspect of parental counseling," which he defines as taking into account all the factors in the family which bear upon the counseling process—the harmony in the marriage, absence of one parent, age and sex of other children, and so on. He states, "The basic point of 'cluster counseling' is that there is no simple, s i n g l e solution," and stresses that counseling r e q u i r e s "realistic, sympathetic human attitudes toward the client and his family." Storrs[4] has stated similar principles in dealing with parents making application for the state institution which he directs: "Medicine is an art, and handling the relatives is one of the important functions of this art. In my opinion, every case is individual and should be investigated as such. I want to know all I can about the child, the family, and all situations connected with both the child and the family. . . . Doctors as a class do not seem to realize the enormity of the tragedy experienced

by the parents when they find that their child is definitely defective. This should be appreciated by all doctors and they should size up the parents. . . I have always felt that it was a mistake not to tell the parents the whole truth. . . . Parents have in many instances been from doctor to doctor, spending their money; have been given evasive answers; have built up hopes over and over, only to have them dashed to the ground, finally. It always seemed to me that they should be told the truth as early as possible—with, as I have said, consideration of the family situation."

Kanner[5] stresses the increasing recognition of the need for "professional and at the same time humane attention" to the parents of retarded children. His list of the questions most commonly asked of him by parents is an excellent summary of the wide range of issues likely to require attention in this situation, and includes questions on causes, impact upon siblings, indications for or against future children, the handling of friends and relatives, available medical treatment, training possibilities, and prognosis. He notes that unequivocal answers frequently cannot be given, and states, "I have never encountered a parent who respected me less because, in answer to the question about the cause of his or her child's retardation, I made no secret of my inability to supply a definite answer. . . . What most of them hope to hear is indeed not so much a piece of etiological wisdom in words of Greek and Latin origin as an authoritative and sympathetic endorsement of themselves, of their human and parental competence, of their right not to blame themselves for what has happened." His approach to the frequent question about additional children is to place the responsibility clearly upon the parents themselves, pointing out the inevitable risk in any birth, and urging that the decision to have additional children must be contingent upon a concomitant freedom from anticipation of disaster. He describes parents' reactions to mental deficiency in a child as variants of three basic types—mature acknowledgement of the actuality and acceptance of the child; disguises of reality with search for either scapegoats upon which to blame the retardation or magic cures; and complete denial of the existence of any retardation. Since these basic attitudes will color all aspects of the care and management of the retarded child, it becomes the obligation of the physician to identify the attitudes present in the parents, and work for a "thorough overhauling" in the direction of mature acceptance.

The large areas of agreement between the counsel of these writers and the feelings expressed by the parents will be immediately apparent. It was of special interest to me that two of the parents referred to two of the authors cited as having provided consultations in the cases of their children, and in both instances the parents described the experiences with enthusiastic praise.

There is a growing tendency to refer retarded children to special clinics for diagnostic evaluation and for treatment recommendations. In communities where such clinics are available, the problem of counseling the parents will be shifted from the

individual practitioner to the clinic staff. However, such facilities remain few in number and inadequate in staff for more than token capacities. The individual physician—the pediatrician, or neurologist, or psychiatrist, or most frequently the general practitioner—will continue to serve as initial counselor for the great majority of parents with retarded children, and must develop appropriate knowledge and skills for this difficult task. The reports of the parents who contributed letters are not felt to reflect the characteristic practices of physicians. They are, however, felt to be of value in providing principles for the correct handling of the initial counseling situation, and these are seen to be in accord with the principles announced by Jensen, Doll, and Kanner in recent contributions to the field.

SUMMARY

Eighty-five letters from parents with retarded children describing the initial experience of the parents on being informed of the diagnosis of mental deficiency have been analyzed from the viewpoint of the parents' feelings concerning the handling of the situation by the physician.

The letters stressed the importance of the physician's attitude, the thoroughness of the study which preceded the announcement of the diagnosis, and the clarity and directness of his communication.

Complaints were lodged against the tendency to stress only the limitations and not the assets of the child, and against the failure to discuss fully the developmental prognosis in both general and specific, day-to-day terms.

The positive role played by religion in their adjustment to the situation was stressed.

Strong condemnation was expressed toward the counsel to institutionalize the child without the physician himself knowing about institutions, and without consideration of the parents' urge to love and care for their retarded children.

Wide agreement was expressed in favor of early announcement of the diagnosis, in preference to temporizing statements to the effect that the child would "grow out of it."

Three recent contributions to the literature have been summarized, and the authors are found to be in close agreement with the parents concerning the principles for the correct handling of the initial counseling of parents with retarded children.

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Comments on Current Literature

PROGRESS REPORT ON ANTIMICROBIAL THERAPY OF TUBERCULOSIS

PHYSICIANS in twenty-two hospitals located in various sections of the country have been cooperating with the United States Public Health Service in a well-controlled investigation of antimicrobial therapy of tuberculosis. The first report of these studies was based on observations made on 1,500 patients who were treated for forty weeks on several therapeutic regimens. The results indicated that, under the controlled conditions obtaining, "isoniazid alone was approximately equal to streptomycin plus para-aminosalicylic acid (PAS), while the combination of isoniazid plus streptomycin was slightly superior to both." Although significantly fewer patients continued to produce sputum positive for tubercle bacilli, in those patients who did continue to produce positive sputum, the acid-fast organisms were almost invariably drug-resistant to streptomycin when streptomycin and PAS were administered, to isoniazid when this drug was the only therapeutic agent employed, and to both streptomycin and isoniazid when both drugs were administered. Clinically the regimens including both streptomycin and isoniazid were thought to give superior results. However, the possible emergence of acid-fast strains resistant to both the principal antituberculosis drugs, streptomycin and isoniazid, prompted the investigating groups to study the effectiveness of isoniazid in combination with PAS, and that of a combination of all three, isoniazid, streptomycin, and PAS.

Accordingly, the protocol for the second large-scale study, which was adopted in March, 1953, included five regimens as follows:

Isoniazid (3 mg. per kg.) plus streptomycin
Isoniazid (3 mg. per kg.) plus PAS
Isoniazid (10 mg. per kg.) plus streptomycin
Isoniazid (10 mg. per kg.) plus PAS
Isoniazid (10 mg. per kg.) plus streptomycin and PAS

"Streptomycin was given in dosages of 1 Gm. twice a week; PAS, 10 to 12 Gm. daily; and isoniazid in doses of 3 or 10 mg. per kg. daily. Only patients with pulmonary tuberculosis who have received no previous antimicrobial therapy are eligible for this second study."

A progress report of this second planned investigation appears in the January, 1954, issue of *The American Review of Tuberculosis*.[1] Thus far only 335 patients have been observed for a period of twenty weeks. The number of patients in the study was limited by certain factors which led the cooperating group to select only those patients satisfying very strict criteria. However, in those patients who were included, the study was well controlled in all aspects, making the results in a comparatively smaller group more significant, or better suited to critical analysis. Of 335 patients selected by the investigating group, 78 are being treated with isoniazid, 3 mg. per kilogram of body weight, plus streptomycin; 64 with isoniazid, 3 mg. per kilogram of body weight, plus PAS; 73 with isoniazid, 10 mg. per kilogram of body weight, plus streptomycin; 63 with isoniazid, 10 mg. per kilogram of body weight, plus PAS; and 57 with isoniazid, 10 mg. per kilogram of body weight, plus streptomycin, plus PAS.

While the results of this cooperative investigation, as reported in the current publication, must be regarded as preliminary, the findings are of such interest that certain aspects of the study merit special comment. Careful bacteriologic smear studies on

sputum specimens indicated that the percentage positive for acid-fast organisms decreased over the period of twenty weeks from a level of 56 to 59 per cent positive to a level of 6 to 15 per cent positive.

By the criterion of bacteriologic culture for the presence of acid-fast organisms, the percentage in all regimens decreased from a range of 71 to 89 per cent positive at the beginning of the study, to one of 9 to 21 per cent by the end of the twentieth week. No significant differences were observed among the five regimen groups, the decline in positive specimens being about comparable.

Objective changes in the chest x-rays were of interest in that the proportion of patients showing moderate or marked roentgenographic improvement increased steadily on all regimens throughout the twenty-week period. Sixty-two to 68 per cent of the patients showed significant roentgenographic improvement by the end of twenty weeks of therapy. Thus, also on the basis of chest findings, all five therapeutic regimens appeared to be effective in bringing about improvement.

Toxic manifestations to isoniazid were noted in nine patients, all receiving 10 mg. of the drug per kilogram of body weight. In these patients symptoms of peripheral neuritis appeared between the forty-second and ninety-fifth days of treatment, or on the average at about sixty-five days. Among the nine, three were able to continue the drug as planned; in two, it was necessary to reduce the dosage; and in four, isoniazid had to be discontinued entirely. At the writing of the progress report, all of the nine patients so affected had improved, or were completely free of toxic manifestations.

The authors are not prepared to make other than tentative conclusions on the basis of the results obtained to date. They believe, however, that the following trends are apparent:

1. Isoniazid and PAS are as effective as isoniazid plus streptomycin.
2. All three antituberculosis drugs in combination are no more effective than either isoniazid and streptomycin, or isoniazid and PAS.
3. There is no evidence thus far that the therapeutic effectiveness of isoniazid increases with increasing dosage. Toxicity to isoniazid was not observed in patients receiving 3 mg. per kilogram of body weight, but among patients receiving 10 mg. per kilogram of body weight, about one in ten developed peripheral neuritis. In about one-third of those affected, this manifestation was severe enough to preclude the further use of isoniazid.

Even when conclusions are considered tentative, progress reports from current investigations are informative, stimulating, and encouraging. Such well-controlled, broad-scale, cooperative ventures as the one being reported give promise of furnishing practicing physicians with a reasonable guide for the use of antituberculosis drugs, a need acutely felt by those in whose communities public health control measures against the spread of tuberculosis are inadequate. However, as the authors emphasize, the results with these antituberculosis drugs must at the present time be considered preliminary. Further progress reports and evaluation by patient follow-up data will be anticipated with interest.

RUSSELL J. BLATTNER.

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Washington, D. C., Feb. 19, 20, and 21, 1954.

Dr. William Curtis Adams, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33, Pa.

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Dr. Lee Roland Ashmun, 913 Windsor Ave., Dayton 7, Ohio.

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Dr. Roy Frank Thagard, U. S. Army Hospital, Camp Polk, La.

Dr. Harry Jacob Umlauf, Jr., Pediatric Service, Brooke Army Hospital, Fort Sam Houston, Texas.

Dr. William R. Watson, 3201st USAF Hospital, Eglin AFB, Fla.

Dr. Charles Richard Webb, 4628 Kenmore Dr., N. W., Washington 7, D. C.

Dr. William Wiley Whitten, 9 Willow Ave., Larchmont, N. Y.

Dr. Dorothy J. York, 4325 Clara St., New Orleans, La.

The following oral examination will be held by the Board:

New York City, April 30, May 1 and 2, 1954.

Dr. Evert Gorter, professor of pediatrics at the University of Leyden from 1923 to 1951, died February 17, 1954. Dr. Gorter had many pediatric friends throughout the world. He was an honorary member of the American Pediatric Society, and made his last visit to the United States in 1947 at the time of the meeting of the V International Pediatric Congress in New York. He made many contributions to the development of pediatrics, and was active in the medical program of the League of Nations. During World War II he was the first professor at the University of Leyden to resign in protest to the Nazi invasion of Holland and was exiled from Leyden to North Holland during the Nazi occupation.

Dr. James G. Hughes, professor of pediatrics, University of Tennessee, College of Medicine, has been appointed pediatric consultant to the European Command of the United States Army, and will visit Army medical installations in Germany and France next August and September. He will evaluate the quality of pediatric services in the various hospitals, serve as consultant, hold conferences on pediatric problems with medical officers, and subsequently turn in a report to the Office of the Surgeon General, U. S. Army. Colonel Hughes is Commanding Officer of the 330th General Hospital in the Active Reserve.

The **University of Louisville School of Medicine** announces the appointment of Dr. Murray M. Lipton as assistant professor of child health research. Dr. Lipton will conduct his virological research in the School's Kentucky Child Health Foundation Laboratory which is under the direction of Dr. Alex J. Steigman, professor of

child health. Dr. Lipton comes to the University from the Public Health Research Institute of New York.

The **Institutes for Physicians and Nurses in the Care of Premature Infants** at The New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, are currently in their fifth year of operation. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses of four weeks' duration. Participants pay no tuition fee and stipends are provided to help cover expenses during attendance at the Institute. The last Institute for the current fiscal year starts on May 17, 1954. Five Institutes will be held between September, 1954, and May, 1955. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 East 68th St., New York 21, N. Y.

Postgraduate Courses in Pediatrics, Harvard Medical School, June 14 to 25, 1954. Two postgraduate courses in pediatrics are being offered by the Department of Pediatrics, Harvard Medical School, at Massachusetts General Hospital in June, 1954. The first, which will be from June 14 through June 22, will deal with general pediatric problems. The second, on June 23 through June 25, will deal with endocrine and metabolic disorders in children and adolescents. Enrollment may be for either course or the total combined course. Those interested should write: Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston, Mass.

The **Third International Poliomyelitis Conference** will be held in Rome, Italy, Sept. 6 to 10, 1954. There will be six chief topics of discussion: Social Aspects, Acute Poliomyelitis, Infection and Immunity, Orthopedics, Physical Medicine and Rehabilitation, and Trends in Poliomyelitis. Physicians interested in polio are invited. Full information, with hotel reservation blanks, may be obtained from the *Secretariate of the Third International Poliomyelitis Conference, Via Lucullo 6, Rome.* Travel arrangements and tours in connection with the Conference may be made through Thomas Cook & Son, 587 Fifth Ave., New York 17, N. Y. The *SS Independence* sails from New York August 26 and arrives at Naples September 14, where a special train will carry members to Rome. There will be simultaneous translation of the papers into English, French, Spanish, German, and Italian.

A **summer camp for diabetic children** will be opened for the sixth season under the auspices of The Chicago Diabetes Association, Inc., from July 18 to Aug. 8, 1954, at Holiday Home, Lake Geneva, Wis. There will be a staff of resident physicians and dietitians, trained in the care of diabetic children, furnished by The Chicago Diabetes Association. Boys and girls, aged 8 through 14 years, are eligible. For further information interested persons should write or phone the office of The Chicago Diabetes Association, 5 South Wabash Ave., Chicago 3, Ill., Andover 3-1861.

Book Reviews

Aarsagerne Til For Tidlig Fødsel (Causes of Prematurity). Svend Nørregaard, Copenhagen, Denmark, 1953, Arne Frost-Hansens Forlag, 240 pages.

A monograph in Danish, with English summary, presenting the author's investigations into the causes of prematurity. The material for the study consists of 1,125 premature infants (weight under 2,500 grams) born in 1948 in Copenhagen. Twenty per cent were twins and in 896 single births labor was induced in 107. Over half of the births occurred at the Rigshospital. A control series comprised 1,000 deliveries, with only 0.5 per cent twins. In 10 per cent, labor was induced.

Numerous factors were studied. There were relatively more premature infants born to mothers under 20 and over 40 years of age. Primigravidas were equally represented in the two series. Mothers with a previous history of a pregnancy ending in miscarriage or premature delivery tend to give birth prematurely, and mothers in the premature series gave family histories of premature birth far more often than in the control series. The premature series contained more mothers in the indigent group and those whose living conditions were unfavorable. Factory workers appeared to be predisposed to premature delivery.

The premature series had a higher percentage of mothers with syphilis and gonorrhea, and with hypertension and albuminuria during pregnancy. There was a much higher incidence of late bleeding. While infections were more frequent in the mothers of the premature series, endocrine disorders occurred in equal frequency in the two series.

Nørregaard found what he terms "provoking factors" in 60 per cent of the mothers in the premature series in individual cases, and in only 20 per cent in the control group. He enumerates the morbid conditions and constitutional and social factors involved as revealed by his study, and states that a combination of two or more factors is often required to bring about a premature delivery.

The graphs in the text have English captions and are clear. The book includes an extensive survey of previous studies on prematurity in all parts of the world, with a bibliography of 255 references.

Aggression, Hostility and Anxiety in Children. Lauretta Bender, Springfield, Ill., 1953, Charles C Thomas, 184 pages. Price $5.50.

This book consists of papers written, for the most part between 1934 and 1940 by the author, Paul Schilder, and other members of the Division of Child Psychiatry, Bellevue Hospital. The papers contain clinical observations on some 260 children and young adolescents, who were patients on the wards of the children's psychiatric service because of various forms of aggressive behavior, deviate, disturbed, or inadequate maturation, and unhappiness. Follow-up data from eight to fifteen years after the original study on over fifty of the children are also included.

The text consists of case studies which include the use of projective techniques, drawings, questionnaires, and interpretations. The material includes, in addition to the subjects indicated in the title, studies on suicide, homicide, firesetting, and death attitudes of children.

The case histories and laboratory data provide valuable factual matter and the clinical interpretations are sound. Unfortunately the text is interspersed with theoretical considerations of questionable validity which detract from an otherwise valuable contribution.

How to Help the Shut-In Child. Margery D. McMullin, New York, 1954, E. P. Dutton & Co., Inc., 192 pages. Price $2.75.

A useful little text by the Executive Director of the Handicapped Children's Home Service in New York. It contains 313 "practical, simple, thoroughly tested suggestions" for helping the child who is bedridden. Few call for any extensive outlay for material or equipment. It is a text that can be recommended to help parents keep the bedridden child as happy and contented as possible under the situation.

Editor's Column

PARENTS OF THE MENTALLY RETARDED CHILD

HOW to inform parents that their child is mentally defective, that he will never achieve a mental status compatible with useful living, a verdict which to many parents is worse than death itself, has been a matter of concern to the physician for many years. The subject was discussed by Jenkins[1] in 1936 and again by Brennemann[2] in 1945. The more recent literature is reviewed by Zwerling.[3]

The subject is one of the first importance to the practicing physician. Unfortunately little direct therapy can be offered for most mentally retarded children, but the physician, by the way he talks to the parents, is in a position to do much to lessen the blow and to advise a reasonable course of action. At least he can avoid hurting the parents unduly by not using terms which offend, like mongolian idiocy, and by using caution about recommending institutional care or urging it too strongly.

A fresh approach to this subject is reported elsewhere in this issue of the JOURNAL by Zwerling (page 469). He turned to the parents of mentally retarded children in order to discover their reactions when they were told by the physician the tragic news about their child's infirmity. He collected his data from letters written by the parents. Since not all the parents replied, the material is not suited for quantitative analysis. Nevertheless the replies contain much useful information.

The most frequent comment in the letters related to the attitude of the physician. Many parents complained about the brusqueness of the physician when he first told them about the condition of their child. On the other hand, several parents voiced dissatisfaction because their physician, out of concern for their feelings, deferred giving a final diagnosis, or because the physician himself seemed overly distressed by the child's condition.

Other points emphasized in the letters are the need for the physician to express himself in terms which the parents can readily comprehend; the importance of the physician being acquainted with available facilities for the management of the retarded child; and the caution to be used in advising institutional care.

Mr. Martin Papish,[4] an officer of the National Association for Retarded Children, has listed the questions which the parents of a retarded child want answered by the physician. They ask first of all, writes Papish, that the doctor be honest with them and tell them as soon as possible that the child is mentally retarded; that an estimate of the child's future potentialities be made whenever possible; that the information be transmitted with due regard to the parents' feelings; that the parents be given all available information and acquainted with all known resources; that the decision as to placing the child in an institution be left up to the family.

Distasteful to parents are the terms "moron," "imbecile," and "idiot," and Papish urges that a new terminology, less offensive to the family and to the community at large, be introduced. Work along those lines is already under way by the American Association on Mental Deficiency.

Kanner,[5] who has contributed much to clear thinking about mental deficiency and its management, lists a number of questions which, in his experience, parents of retarded children want answered. The parents are concerned about the hereditary aspects of the condition; the possibility of future children being similarly afflicted; the possibility of their normal children becoming feeble-minded; the effect of a retarded child in the home on the other children; how to explain the patient's condition to his siblings; what explanation to make to neighbors; whether anything can be done to accelerate mental development, such as an operation or glutamic acid or other drugs; how much further the child will develop; what school progress can be expected; whether home or institution is better and, if an institution, which one; how long he will have to stay in an institution; whether he will be able to marry; and whether he should be sterilized?

Few things in medical practice require more human understanding and compassion than the problem of informing parents that their infant or young child is mentally retarded. It is essential that they be told, but the news can be tempered with kindness and hopefulness until the parents have had time to adjust themselves to the tragedy. Perhaps what helps most is to make the honest statement that, in a young infant, it is impossible to foretell the exact amount of retardation that will eventually be present, and that many have turned out better than was thought probable at this early age. The importance of working to bring out the latent potentialities as far as possible and the danger of allowing the infant to vegetate, through a feeling of helplessness, should be stressed. Such problems as sibling relationship, institutionalization, and the like will come up automatically later on when the parents have, to some extent, become adjusted to the situation, and hence need not be discussed at this time. Most important, it should be emphasized that neither parent is to blame. It is difficult to think of any other situation where help is more needed, and which calls for the humanitarianism which has made the word "physician" respected over the ages.

H. B.

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OXYGEN AND RETROLENTAL FIBROPLASIA

IN AN editorial discussion in the January issue (page 122) of the experimental work of Ashton and his co-workers, linking oxygen with the development of retrolental fibroplasia, it was noted that other as yet unreported experimental studies were in progress. In a recent issue of the *American Journal of Ophthalmology,* Patz, Eastham, Higginbotham, and Klek[1] report on experimental studies using newborn white rats and mice. In one of their experiments, litters of rats were exposed to an oxygen concentration of 80 per cent, while control litters were maintained in a concentration of 20.8 per cent. At the end of twenty-one days, 12 of 27 rats exposed to the high concentration showed vascular changes and edema in 17 eyes, while no changes were detected in 58 eyes of the control group of 29 animals. In another experiment, litters of white mice were exposed to the high concentration for periods of seven, fourteen, and twenty-one days, with control litters of similar size exposed to a low concentration. In a group of 36 mice exposed for seven days there were 21 abnormal eyes, while none were found in the control group. After fourteen days of exposure, 41 abnormal eyes were found in 34 animals, and 2 in the control group of 33. The number of abnormal eyes rose to 71 in 38 animals exposed for twenty-one days, while none were found in 37 control animals. The changes were chiefly capillary proliferation and hemorrhage, "strikingly similar to the changes detected in human retrolental fibroplasia."

Thus evidence continues to accumulate that the oxygen concentration to which the small premature infant is exposed in the incubator is related to the development of retrolental fibroplasia. In these experiments length of exposure is indicated as a factor.

From their clinical and experimental data, Patz and his co-workers feel that certain recommendations in the care of the premature infant are justifiable—the practice of rigid curtailment of oxygen therapy for the premature infant; an accurate oxygen analyzer as standard nursery equipment, with frequent sampling of the oxygen tension of the incubator; the ordering of oxygen by concentration rather than the rate of flow, and the use of oxygen in the nursery only on specific order, except in case of emergency. These are in line with the recommendations referred to in the previous editorial.

The importance of retrolental fibroplasia as a cause of blindness in the preschool child is stressed in a recent report of the National Society for the Prevention of Blindness. Blindness in this group increased 47 per cent between 1943 and 1950. Most of this increase was due to retrolental fibroplasia. Between these two dates blindness from prenatal influences decreased from 12.9 cases per 100,000 children to 8.5; blindness from infections decreased from 2 to 1; blindness from injuries fell from 1.1 to 0.6; but blindness due to retrolental fibroplasia increased from 1.4 to 10.9. Over 95 per cent of the blindness in preschool children takes place before the infant is a year old.

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